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# Acute Lymphoblastic Leukemia in Children and Teens

Revised 2022

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## A six-word narrative about living with blood cancer from patients in our LLS Community

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**Stay strong and keep moving forward. Find the positive in every day.**  
**Be your own best patient advocate. Changed my life for the better.**  
**Accept, learn and focus on present. Learning to live a different life.**  
**Sudden and life changing—be positive. Waiting, worrying, anxiousness/happy I'm alive!** Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. **Patience, positive attitude, hope and faith. Test to test, I will survive!** Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. **So far, so good, live life.** Meditation, mindfulness, wellness, faith, nutrition and optimism. **Finding the joy while living with uncertainty.** Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! **Eye opening needed learning and healing.** Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. **Thank god for stem cell transplants!** Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. **Embrace your treatment day after day.** Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. **Live life in a beautiful way.**



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Join our online social network for people who are living with or supporting someone who has a blood cancer. Members will find:

- Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff
- Accurate and cutting-edge disease updates
- The opportunity to participate in surveys that will help improve care

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#### **Elizabeth A. Raetz, MD**

KiDS of NYU Foundation Professor of Pediatric Medicine  
NYU Grossman School of Medicine  
Director, Division of Pediatric Hematology/Oncology  
NYU Langone Health  
New York, NY

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# Introduction

This book provides information about acute lymphoblastic leukemia (ALL) in children and teens. Acute lymphoblastic leukemia is also known as “acute lymphocytic leukemia” and “acute lymphoid leukemia.”

People of all ages, from infancy to the elderly, can develop ALL. About half of ALL cases are diagnosed in children. It is the most common childhood cancer in the United States. An average of 2,826 children and young adults (younger than age 20) were diagnosed with leukemia each year from 2014 to 2018 in the United States.\*

Over the past decades, survival outcomes for children with ALL have improved dramatically. Childhood ALL now has one of the highest cure rates of all childhood cancers. Today, most young patients diagnosed with ALL can expect to have full and productive lives after treatment. Many survivors return to school, attend college, enter the workforce and become parents.

However, more work remains to be done. New therapies are being studied in clinical trials to find cures for every child who has ALL, including those with high-risk disease and those who relapse after treatment.

This book provides medical information about ALL as well as advice to help you, your child and your family cope. We trust that this information will provide you with a good working knowledge of ALL and that it reinforces what you already know. We hope that you will keep this book handy and, should you ever feel alone when confronting problems, that you will turn to it for information and guidance to find the support and resources you need.

\*Source: SEER (Surveillance, Epidemiology, and End Results) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)), Cancer Statistics Review, 1975-2019. National Cancer Institute; 2021.

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# Leukemia

Leukemia is a type of cancer. Cancer is a term for diseases in which abnormal cells grow uncontrollably and can spread to other parts of the body. Cancer can start almost anywhere in the body. Leukemias are cancers that begin in cells that would normally develop into blood cells.

Most blood cells are made in the bone marrow. Bone marrow is the spongy tissue in the center of the bones. There are three main types of blood cells: red blood cells, white blood cells and platelets. Red blood cells carry oxygen throughout the body. White blood cells help fight infections. Platelets help stop bleeding by clotting (clumping together) at the site of an injury.

Inside the bone marrow, there are blood stem cells, called “hematopoietic” stem cells, which are immature cells that can develop into all types of blood cells. A blood stem cell goes through many stages before it eventually develops into a red blood cell, a white blood cell or a platelet.

Leukemia begins in one of the immature blood cells in the bone marrow. One or more mutations (changes) occur in the DNA of the cell, and it becomes a type of cancer cell, called a “leukemia cell.”

Leukemia cells do not mature into healthy, functioning blood cells. They grow more quickly and live longer than normal blood cells. They divide and copy themselves to make more and more leukemia cells. Over time, the leukemia cells crowd out and suppress the development of healthy blood cells in the bone marrow, and they spill out of the bone marrow into the bloodstream.

The four major types of leukemia are:

- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)
- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)

Doctors classify leukemia based on disease progression (meaning how quickly the disease gets worse) and the type of blood cells involved. Leukemias can be “acute” or “chronic.” Acute leukemias develop and progress rapidly and usually get worse quickly if they are not treated. Chronic leukemias tend to progress more slowly. Acute leukemias are much more common in children than chronic leukemias.

Leukemia is also classified by the type of blood cell that becomes cancerous. In the body, normal blood stem cells develop into two primary types: lymphoid stem cells and myeloid stem cells. As lymphoid stem cells mature, they become a type of white blood cell called a “lymphocyte.” Myeloid stem cells eventually become

red blood cells, platelets or other types of white blood cells (basophils, eosinophils, monocytes and neutrophils). If the cancer begins in a lymphoid cell, the leukemia is called “lymphocytic” or “lymphoblastic” leukemia. If the cancer starts in an early form of a myeloid cell, the cancer is called “myeloid” or “myelogenous.”

**For general information about ALL, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to view the free LLS book *The ALL Guide: Information for Patients and Caregivers*.**

## Acute Lymphoblastic Leukemia

**How Acute Lymphoblastic Leukemia (ALL) Develops.** ALL is a type of cancer in which the bone marrow makes too many immature lymphocytes, a type of white blood cell. Lymphocytes begin in the bone marrow as a lymphoid stem cell. A normal lymphoid stem cell becomes a lymphoblast that eventually develops into a lymphocyte. There are three major types of lymphocytes: B cells, T cells and NK cells.

In people with ALL, a mutation or a series of mutations in the DNA (genetic material) of the lymphoid stem cell results in the formation of a leukemic lymphoblast that is stuck in the earliest stage of cell development. This leukemia cell, also referred to as an “ALL blast” or “ALL cell,” cannot mature into a fully functioning lymphocyte that helps fight infection.

Genetic errors in the lymphoblast cause the cell to keep growing and dividing, whereas a healthy cell would stop dividing and eventually die. Every cell that arises from the initial leukemia blast cell also has the mutated DNA. As the leukemia cells multiply uncontrollably and quickly accumulate in the bone marrow, they slow down or stop the production of normal, healthy red blood cells, white blood cells and platelets. As a result, there are too many immature leukemic blast cells that cannot fight infection and too few mature, functional red blood cells, white blood cells and platelets.

Over time, the leukemia cells spill out of the bone marrow into the bloodstream. This can cause the number of white blood cells in the blood to increase, but most of these are leukemia cells that do not protect against infection. Once in the blood, the leukemia cells can spread to other parts of the body such as the central nervous system (brain and spinal cord) or testicles.

By the time ALL is diagnosed, the number of healthy red blood cells, white blood cells and platelets is usually lower than normal. Having low levels of blood cells may result in infections, anemia, and excessive bleeding or bruising.

<b>Medical term:</b>	<b>Description:</b>
Anemia	Low red blood cell count
Thrombocytopenia	Low platelet count ("thrombocyte" is another word for platelet)
Neutropenia	Low neutrophil count (a neutrophil is a type of white blood cell)

This book focuses on ALL, but there are other cancers, called "lymphomas," that also begin in lymphoid cells. Most lymphomas arise from more mature lymphoid cells, but in rare instances they can develop from lymphoblasts. The main difference between lymphoblastic leukemias and lymphoblastic lymphomas is the location of the cancer cells. Leukemias such as acute lymphoblastic leukemia (ALL) are usually found in bone marrow and blood. In contrast, lymphomas are primarily located in lymph nodes or other lymphatic tissues or organs. Patients with acute lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy. So if your child has been diagnosed with acute lymphoblastic lymphoma, this book should be helpful for you.

## Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of disease. A "sign" is a change that the doctor sees during an exam or in a laboratory test result. A "symptom" is a change that a patient can see or feel.

A person who has signs or symptoms that suggest the possibility of leukemia is referred to a specialist called a hematologist-oncologist. This is a doctor who has special training in diagnosing and treating blood disorders and blood cancers such as leukemia, lymphoma and myeloma. A pediatric hematologist-oncologist specializes in the care of children with blood disorders and blood cancers.

It is common for someone with ALL to feel a loss of well-being because of the lack of normal, healthy blood cells. This happens when the leukemia cells in the bone marrow crowd out the normal blood-making cells. Your child's blood counts may show a high number of white blood cells, but if your child has ALL, these cells are not fully developed and do not fight infection well. With ALL, the leukemia cells begin to reproduce very quickly and compete with the other healthy blood cells for nutrients and space. Consequently, children with ALL may not have enough mature red blood cells, white blood cells and/or platelets, and often have symptoms related to low blood cell counts.

Symptoms of anemia (low red blood cell count) include:

- Fatigue
- Shortness of breath during normal physical activities
- Dizziness
- Pale complexion

Symptoms of neutropenia (low number of neutrophils, a type of white blood cell important in fighting infections) include:

- Frequent infections
- Recurrent fevers

Symptoms of thrombocytopenia (low platelet count) include:

- Bruising easily
- Prolonged bleeding from minor cuts
- The appearance of pinhead-sized red spots on the skin, called “petechiae”
- Frequent or severe nosebleeds
- Bleeding gums
- In females, heavier or more frequent menstrual periods

Symptoms may also be related to leukemia cells collecting in other parts of the body. These symptoms may include:

- Unexplained weight loss or loss of appetite
- Night sweats
- Pain in bones and joints
- Swollen lymph nodes
- Enlarged spleen or liver
- Abdominal pain
- Wheezing, coughing or painful breathing

It is important to note that the signs and/or symptoms of ALL may be similar to those of other diagnoses. Speak with your doctor if your child has any of the above symptoms, to ensure proper diagnosis and treatment.

## Diagnostic Testing

While certain signs and symptoms may indicate that a person has ALL, lab tests are needed to confirm the diagnosis. It is important to have an accurate diagnosis, because it helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

### **Talk to your doctor about**

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the test results

Some of the tests may be repeated both during and after treatment to evaluate if treatment is working.

**Medical History.** Your child's doctor will take a thorough medical history. The doctor will ask about any health problems or treatments that your child has had. The history may include information about past illnesses, injuries, other treatments and medications. Some illnesses run in families, so the doctor may also ask about the health of your child's blood relatives.

**Physical Examination.** The doctor will want to know about your child's current symptoms and will conduct a physical examination. During the examination, the doctor may listen to your child's lungs and heart, and carefully examine the body for signs of infection and disease. To check the internal organs, the doctor may also feel different parts of your child's body. For example, the doctor may feel the abdomen to see if your child has an enlarged liver or spleen. Because ALL can cause enlarged lymph nodes, the doctor may check your child's lymph nodes in the neck and armpits. In males, the doctor may also examine the testicles to see if there are any masses.

**Complete Blood Count (CBC) with Differential.** This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample. Children with ALL often have a high number of white blood cells, but most of these are leukemia blast cells that do not protect against infection. Meanwhile, they may not have enough mature white blood cells, red blood cells or platelets. Even if the CBC findings suggest leukemia, an ALL diagnosis is usually only made after examination of a sample of bone marrow cells, which can be obtained with bone marrow aspiration and biopsy (see below).

**Bone Marrow Aspiration and Biopsy.** Leukemia begins in the bone marrow. To diagnose ALL, samples of bone marrow must be removed and tested for leukemia cells. The procedure is generally done at the doctor's office or in a hospital. Most children are under sedation or general anesthesia during the procedure. The samples are usually taken from the top part of the back of the hip bone.

Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special hollow biopsy needle is inserted through the hip bone and into the bone marrow to aspirate (remove) a liquid sample of bone marrow cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope. See **Figure 1** on page 8.

## Figure 1. How Are the Blood and Bone Marrow Tests Done?

**Blood Test.** Blood is taken from the patient's arm with a needle. The blood is collected in tubes and sent to a lab for testing.

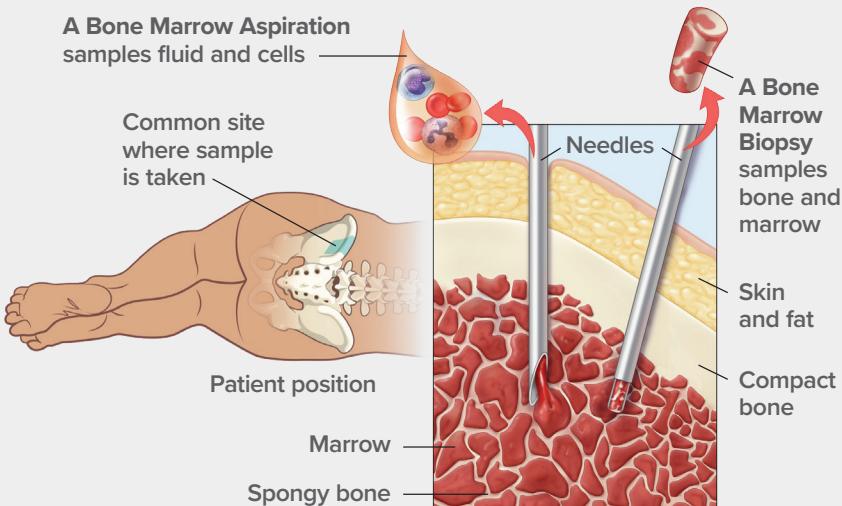
**Bone Marrow Aspiration.** A sample of fluid with cells is removed from the bone marrow and sent to a lab for testing.

**Bone Marrow Biopsy.** A very small amount of bone filled with bone marrow cells is taken from the body and sent to a lab for testing.

Both bone marrow tests are done with special needles. Adults and older teens may be given a local anesthetic and be "awake" during this procedure, but most children are under sedation or given general anesthesia, which makes them "sleep" briefly during the tests. The sample of cells is usually taken from the back of the patient's hip bone.

Blood and bone marrow tests may be done in the doctor's office or in a hospital. A bone marrow aspiration and biopsy are almost always done at the same visit. Blood and bone marrow tests may be done both during and after treatment. The tests are repeated to see if treatment is working.

### Bone Marrow Aspiration and Biopsy

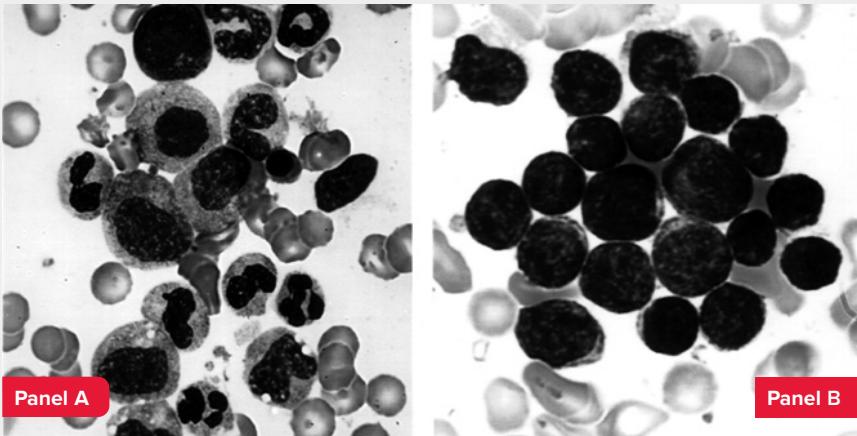


**Left:** The place on the back of the patient's hip bone where a bone marrow aspiration or biopsy is done. **Right:** Where the needle goes inside the bone to collect the liquid sample for aspiration and the bone sample for biopsy. The needles are different sizes for each of these tests.

**Cell Assessment.** At the lab, a hematopathologist examines the blood and bone marrow samples. A hematopathologist is a doctor who has special training in identifying blood diseases by studying cells under a microscope.

The hematopathologist examines the blood and bone marrow cells under a microscope to determine their size, shape and type, as well as to identify other cell features. Whether the cells look like normal, mature blood cells or abnormal, immature blood cells (blast cells) is an important finding. See **Figure 2**, below.

**Figure 2. Acute Lymphoblastic Leukemia (ALL) Cells**



**Panel A** shows a photograph of developing cells in healthy marrow. The variation in the appearance of the cells is characteristic of normal bone marrow. **Panel B** shows a photograph of bone marrow cells from a patient with acute lymphoblastic leukemia. An unvaried appearance characterizes the leukemic blast cells.

The percentage of blast cells identified in the samples is another important finding. Typically, there are no blast cells in the blood, and no more than 5 percent of the cells in the bone marrow are blast cells. Generally, a diagnosis of ALL in children requires a finding of 25 percent or more lymphoblasts in the bone marrow.

If leukemia is found, additional tests are done on the blood and bone marrow samples to gather information about the subtype of ALL.

**Flow Cytometry.** This lab test studies the antigens, or proteins, on the surface and within the cancer cells. Finding, or not finding, certain proteins can help the hematopathologist determine the type of leukemia. The pattern of the surface proteins is called the “immunophenotype.”

A bone marrow sample is often used for this test, but it can also be done with a blood sample. The sample of cells is treated with special antibodies created in a laboratory that only bind to cells that have a specific antigen on them.

Depending on the type of leukemia, the leukemia cells can have different antigens on their surfaces. Certain antigens, called “cluster of differentiation (CD) proteins,” are helpful in identifying leukemia cells.

Flow cytometry helps to confirm an ALL diagnosis. It is also used to determine the type of lymphocytes (B cells or T cells) in which the disease originated, and to assess the maturity of the cells. In addition, flow cytometry is used to check treatment results.

**Genetic Tests.** Cancer is a disease caused by mutations (changes) to the genetic material inside cells. This genetic material is called DNA (deoxyribonucleic acid). Inside the cells, DNA is packaged into thread-like structures called “chromosomes.” Each person’s cancer has a unique combination of genetic mutations.

Genetic testing should be done when the cancer is first diagnosed and may also be indicated after a relapse. This is because it is possible for patients to acquire additional genetic abnormalities after the completion of their initial treatment.

The following tests are used to examine the chromosomes and genes in your child’s leukemia cells.

**Cytogenetic Analysis.** In this test, a hematopathologist or other specialist uses a microscope to examine the chromosomes inside cells. In patients with ALL, cytogenetic analysis is used to look for abnormal changes in the chromosomes of the leukemia cells.

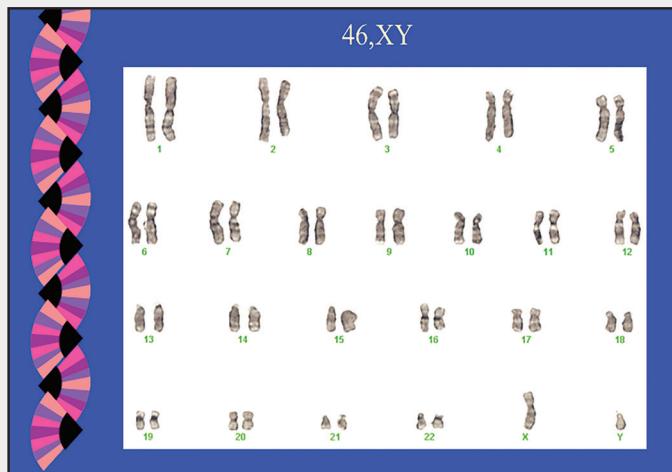
Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. In many cases of ALL, the chromosomes of leukemia cells have abnormal changes that can be seen under a microscope. These abnormalities can be “numerical” or “structural.”

A “numerical abnormality” occurs when there is a different number of chromosomes than are usually found. For example, instead of the typical 46 chromosomes, there may be 45 or 47 chromosomes. A “structural abnormality” means a chromosome’s structure has been altered. One type of structural abnormality is a “translocation.” A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. Sometimes pieces from two different chromosomes break off and trade places. This results in a “fusion gene,” an abnormal gene formed when two different genes fuse together.

Cytogenetic testing can be done with either a bone marrow sample or a blood sample. The leukemia cells in the sample are allowed to grow in the laboratory and then are stained prior to examination. The stained sample is examined under a microscope and photographed to show the arrangement

of the chromosomes, called a “karyotype.” The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the leukemia cells. See **Figure 3**, below.

**Figure 3. Normal Male Karyotype**



This figure shows a normal male karyotype. Courtesy of Dr. Dong Chen, hematopathologist, Mayo Clinic, Rochester, MN.

Cytogenetic analysis provides information for determining a patient’s prognosis (predicted outcome) and treatment options. This information can tell how the disease will respond to treatment. For example, a translocation between chromosomes 9 and 22 is associated with a diagnosis of Philadelphia chromosome-positive (Ph+) ALL, a subtype of ALL treated differently from other subtypes. See page 37 for more information on Ph+ ALL.

**Fluorescence in Situ Hybridization (FISH).** This very sensitive test is used to examine genes or chromosomes in cells and tissues. Doctors use FISH to detect certain abnormal changes in the chromosomes and genes of leukemia cells. Pieces of DNA that contain special fluorescent dyes are prepared in the laboratory and added to the leukemia cells on a glass slide. The pieces of DNA that bind to certain genes or areas of chromosomes light up when the slide is viewed under a specialized “fluorescence” microscope. Not only can FISH identify most abnormal changes that can be seen with a microscope, but it can also detect some changes that are too small to be seen with basic cytogenetic testing. However, it is not used as a general screening tool. FISH has one disadvantage—the doctor must select the specific chromosomes or genes to examine before the test is performed.

**Polymerase chain reaction (PCR).** This very sensitive test is used to detect and measure certain genetic mutations and chromosomal changes that cannot

be seen with a microscope. PCR essentially amplifies (increases) small amounts of specific pieces of either RNA (ribonucleic acid) or DNA (deoxyribonucleic acid) to make them easier to detect and measure in a cell sample. This test can find a single leukemia cell among more than 100,000 normal cells. PCR is one method used to measure minimal residual disease (MRD), which refers to the small amount of cancer cells that may remain in the patient's body after treatment. A PCR test can be done with either a bone marrow sample or a blood sample.

**Next-generation sequencing.** This technique refers to several different laboratory tests that can rapidly examine the exact sequence (order) of DNA or RNA. This makes it possible to identify a variety of genetic alterations in a patient's cancer cells. These alterations are important in guiding risk assessment and prognosis, and may also guide treatment decisions. Next-generation sequencing may help determine which patients are at high risk and may need more intensive treatment or who may benefit from treatment with novel therapies. The number of mutated genes that can be detected in ALL patients has increased considerably with the availability of next-generation sequencing.

**See the free LLS books *Understanding Genetics* and *Understanding Lab and Imaging Tests* for more information about these tests. Visit [www.LLS.org/3D](http://www.LLS.org/3D) to view interactive 3D illustrations of some lab and imaging tests.**

## Diagnosis and Cell Classification

In children, a diagnosis of ALL generally requires a finding that 25 percent or more of the cells in the bone marrow be lymphoblasts. Doctors divide ALL into subtypes based on the type of lymphocytes that are affected and genetic features of the leukemia cells. The ALL subtype is determined based on the results of your child's lab tests.

**Subtypes of ALL.** The subtypes of ALL are identified based on certain features of the leukemia cells. Determining the ALL subtype is an important factor in treatment planning. The doctor will discuss with you which drug combinations and "protocols" are indicated based on your child's ALL subtype. (In medicine, a protocol is a detailed plan of treatment and procedures.) The doctor may also talk about whether a clinical trial may be an appropriate treatment option.

**Immunophenotyping.** Leukemia cells can be classified by the antigens, known as "immunophenotypes," found on their surfaces. The World Health Organization (WHO) classifies ALL based on the immunophenotype of the leukemia cell in the following ways (see **Table 1** on page 13):

- B-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into B cells. If a child's bone marrow has

(con't on page 14)

**Table 1. World Health Organization Classification of Acute Lymphoblastic Leukemia (ALL)**

**B-cell lymphoblastic leukemia/lymphoma**

B-cell lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)

B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

B-cell lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); *BCR-ABL1*

B-cell lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged

B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*

B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy

B-cell lymphoblastic leukemia/lymphoma with hypodiploidy

B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); *IL3-IGH*

B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*

*Provisional entity: B-cell lymphoblastic leukemia/lymphoma, BCR-ABL1-like*

*Provisional entity: B-cell lymphoblastic leukemia/lymphoma with iAMP21*

**T-cell lymphoblastic leukemia/lymphoma**

*Provisional entity: early T-cell precursor lymphoblastic leukemia*

*Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma*

Abbreviations: t, translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half); v, variable.

Source: World Health Organization (WHO). Classification of Acute Lymphoblastic Leukemia Types. 2016.

25 percent or more lymphoblasts, it is called B-cell lymphoblastic leukemia (B-cell ALL). If the lymphoblasts are restricted to a mass in a lymph node or other lymph tissue, and less than 25 percent of the bone marrow cells are lymphoblasts, it is called B-cell lymphoblastic lymphoma. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens rather than traditional lymphoma therapy.

B-cell ALL is the most common ALL subtype, accounting for approximately 80 percent of cases among children with ALL. Within the B-cell lineage, the cell surface markers (proteins) differ according to the stage of cell maturation.

Before 2008, the WHO classified B-cell lymphoblastic leukemia as “precursor B-lymphoblastic leukemia.” This older term is sometimes used to distinguish B-cell ALL from mature B-cell ALL. Mature B-cell ALL is now referred to as “Burkitt leukemia.” The treatment for Burkitt leukemia is based on therapy for non-Hodgkin lymphoma and is very different from the treatment used for ALL.

**For more information on non-Hodgkin lymphoma, see the free LLS book *Non-Hodgkin Lymphoma*.**

- T-cell lymphoblastic leukemia or lymphoma. This subtype begins in immature cells that would normally develop into T cells. If the bone marrow has 25 percent or more lymphoblasts, the disease is called T-cell lymphoblastic leukemia (T-cell ALL). If the bone marrow has less than 25 percent lymphoblasts and the lymph nodes are enlarged, it is called T-cell lymphoblastic lymphoma. This subtype is less common than B-cell ALL and occurs more often in adults than in children. T-cell ALL accounts for approximately 15 to 20 percent of ALL cases in children.

**Genetic Changes.** In addition to classifying ALL as either B-cell or T-cell, it can be further classified based on changes to certain chromosomes and genes (see **Tables 2** and **3** on pages 15–17). Researchers have found that for patients with B-cell ALL, some genetic mutations respond better to treatment than others. The identification of specific genetic abnormalities for patients with B-cell ALL is critical for disease evaluation, risk stratification and treatment planning. While researchers have also identified specific genetic abnormalities in T-cell ALL, these abnormalities are not currently used in the routine diagnosis and treatment planning (although they may represent important targets in the future).

About 75 percent of childhood cases of ALL can be classified into subgroups based on chromosomal abnormalities and genetic mutations. Not all patients who have ALL exhibit the same genetic changes. Some changes are more common than others, and some have a greater effect on the patient’s prognosis.

**See the free LLS book *Understanding Genetics* for more information about genetics and genetic testing.**

**Table 2. Common Genetic Alterations in Childhood B-Cell ALL**

Genetic Subtype	Common Alterations	Frequency in ALL	Prognosis
Abnormalities in chromosome number			
High hyperdiploidy (51-67 chromosomes)		25%	Favorable
Low hyperdiploidy (47-50 chromosomes)		14%	Previously unfavorable, now intermediate
Hypodiploidy (<44 chromosomes)	Near-haploidy (24-31 chromosomes), low-hypodiploidy (32-39 chromosomes)	1-2%	Unfavorable
Recurrent chromosomal translocations			
t(12;21)(p13;q22)	<i>ETV6-RUNX1 (TEL-AML1)</i>	20%	Favorable
t(1;19)(q23;p13.1)	<i>TCF3-PBX1 (E2A-PBX1)</i>	4%	Intermediate
t(17;19)(q22;p13)	<i>TCF3-HLF</i>	<0.5%	Unfavorable
<i>KMT2A (MLL) rearrangements</i>		5-6%	Unfavorable (infants), Intermediate (non-infants)
t(1;11)(q21;q23)	<i>KMT2A-MLLT11</i>		Less unfavorable
t(4;11)(q21;q23)	<i>KMT2A-AFF1 (AF4)</i>		Particularly unfavorable
t(9;11)(p22;q23)	<i>KMT2A-MLLT3 (AF9)</i>		
t(10;11)(p12;q23)	<i>KMT2A-MLLT10 (AF10)</i>		
t(11;19)(q23;p13.3)	<i>KMT2A-MLLT1 (ENL)</i>		

**Table 2 (continued).**

Genetic Subtype	Common Alterations	Frequency in ALL	Prognosis
Other fusion partners			
t(9;22)(q34;p11.2)	<i>BCR-ABL1</i>	3-5%	Unfavorable prior to TKI therapy; Intermediate with TKI therapy?
Other			
Ph-like	<i>IGH-CRLF2, P2RY8-CRLF2</i>	7-8%	Unfavorable
	<i>ABL1, ABL2, CSF1R, PDGFRB</i> rearrangements	5-6%	Unfavorable
	<i>EPOR, JAK2</i> rearrangements	2%	Unfavorable
Trisomy 21-associated ALL	<i>P2RY8-CRLF2, JAK2</i> mutations	50-60% of DS-ALL	Intermediate
iAMP21	Multiple copies of <i>RUNX1</i>	2%	Unfavorable
<i>DUX4</i> rearrangements	<i>IGH-DUX4, ERG-DUX4</i>	3-7%	Favorable
<i>MEF2D</i> rearrangements	<i>MEF2D-BCL9, MEF2D-HNRNPUL1</i>	3-6%	Unfavorable
<i>ZNF384</i> rearrangements	<i>EP300-ZNF384</i>	4%	Intermediate

Note that percentages may total more than 100% due to co-occurrence of genetic lesions.

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; DS-ALL, Down syndrome-associated ALL; iAMP21, intrachromosomal amplification of chromosome 21; TKI, tyrosine kinase inhibitor; t, translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half).

Adapted from Tasian SK, Hunger SP. Genomic characterization of paediatric acute lymphoblastic leukaemia. *British Journal of Haematology*. 2017;176:867-882.

**Table 3. Common Genetic Alterations in Childhood T-Cell ALL**

<b>Genetic Subtype</b>	<b>Common Alterations</b>	<b>Frequency in T-ALL</b>	<b>Prognosis</b>
Recurrent chromosomal translocations			
t(10;14)(q24;q11)	<i>TLX1 (HOX11)</i> fusions	5-10%	Favorable
t(7;19)(q34;p13)	<i>LYL1</i> fusions	10%	Unfavorable
t(1;14)(p32;q11), t(1;7) (p32;q34), t(11;14)(p15;q11), t(11;14)(p13;q11)	<i>TAL1, LMO1, LMO2</i> fusions	50-60%	Unfavorable
t(11;14)(p15;q11), t(5;14) (q35;q32)	<i>TLX3 (HOX11L2)</i> fusions	20-25%	Unfavorable (some studies), Intermediate (some studies), Favorable (some studies)
t(8;14)(q24;q11)	<i>TRA-MYC, TRC-MYC</i>	1%	Probably unfavorable
7p15 translocations	<i>HOXA10, HOXA9</i> overexpression	3%	Unfavorable
KMT2A (11q23) rearrangements	<i>KMT2A-AFF1, KMT2A-MLLT1</i>	5%	Possibly favorable
t(10;11)(p13;q21)	<i>PICALM-MLLT10 (CALM-AF10)</i>	5-10%	Unfavorable (some studies), Intermediate (other studies)
t(9;14)(q34;q32)	<i>NUP214-ABL1</i>	5-15%	Unfavorable (some studies), Intermediate (other studies)
NOTCH1 mutations		50-60%	Favorable
ETP		10-15%	Unfavorable (some studies), Intermediate (other studies)
<i>FBXW7</i> mutation		15%	
Other T-ALL		6%	

Note that percentages may total more than 100% due to co-occurrence of genetic lesions.

Abbreviations: T-ALL, T cell-acute lymphoblastic leukemia; ETP, early thymic precursor or early T-cell precursor; t, translocation between chromosomes; q, the long arm of a chromosome (the lower half); p, the short arm of a chromosome (the upper half).

Adapted from Tasian SK, Hunger SP. Genomic characterization of paediatric acute lymphoblastic leukaemia. *British Journal of Haematology*. 2017;176:867-882.

**Learning About Your Child's Diagnosis.** You are likely to experience a wide range of emotions from the time your child is diagnosed with cancer, through treatment and after. These emotions may include shock, denial, fear, anger, guilt and sadness. You may feel that life for your child and family will never be the same. Allow yourself to feel sad. Understand that you are not to blame for your child's diagnosis.

Over time, you and your family will find ways to adapt and gradually develop a new sense of normalcy. All these feelings are to be expected, but if you feel consumed by negative feelings and emotions or are unable to function, seek professional help. Psychologists, social workers and religious or spiritual advisers may help you come to terms with your child's diagnosis. It is important to work through your feelings so you can help your child cope and you can continue to manage other aspects of family life and work.

**Talking to Your Child About the Diagnosis.** Regardless of age, children are usually aware when their health causes their parents concern. Your child may experience a variety of emotions, such as anger, guilt, fear, anxiety and sadness, possibly all in quick succession.

Sometimes parents wish to shield their child from information about the illness and its treatment. Keep in mind that children will use their imagination to fill in perceived gaps of information. Sharing information about the illness and treatment helps your child build trust in both you and the members of the treatment team, so that your child feels comfortable talking about fears and concerns. Encourage your child to talk about their concerns and ask questions.

Introduce your child to treatment team members who can provide psychosocial support. These include psychologists, social workers, art or play therapists and child-life specialists. In addition to helping you explain the illness and its treatment to your child, they can help your child better understand their disease through play or other activities.

Keep the discussion age-appropriate when you talk to your child about his or her diagnosis. Consider the following guidelines, organized by age:

#### **Baby/Toddler (0 to 3 Years)**

- Children this young do not have an understanding of illness or cancer. However, they are aware of changes to routines and the feelings of people around them.
- Children in this age-group may be afraid of the medical staff and medical procedures.
- Babies and toddlers may be afraid of abandonment or being left at the hospital. Offer physical and verbal reassurance.

### **Preschool/Kindergarten (4 to 6 Years)**

- Children may have some understanding of an illness, such as a cold, but may not grasp the implications of a serious illness.
- Children's primary focus will be the symptoms they are experiencing at any specific moment.
- Children in this age group may be afraid of pain, so explain tests or treatments to them in advance.
- Assure your child that they did nothing wrong and did not cause the cancer.

### **Elementary/Middle School (7 to 12 Years)**

- Children in this age group may have a better understanding of serious illness, but not specifically cancer.
- They may have heard things about cancer at school, from friends, on TV, or they may have found information online. Ask your child what he or she knows and correct any misunderstandings, especially those that cause distress.
- Explain tests, treatments, and other medical procedures in advance. Your child may be afraid of pain and resist some tests or procedures. Be honest. If a procedure might be painful, work with the healthcare team and decide how to explain what will be done to lessen their pain and why the procedure is important.
- Talk to your child in advance about possible changes to their physical appearance.
- You may need to discuss fertility preservation with your child. Some cancer treatments may affect fertility. Fertility preservation, such as egg or sperm banking, may be an option for children who have begun puberty. Fertility preservation needs to be done before treatment begins. Enlist members of the healthcare team to help with this sensitive discussion.
- You may see signs of regression in your child's behavior, such as thumb sucking, bed-wetting or tantrums.
- A child may use play to process the information—play-acting doctor/patient scenarios, for example.
- If the cancer treatment will result in any changes to your child's daily routine, explain the changes ahead of time so that your child will know what to expect.

## **High Schoolers/Teenagers (13 to 18 Years)**

- Teenagers are usually able to understand complex information about their cancer and may want to know more. You may still need to correct any misinformation your teenager has heard about cancer from school, friends, TV and movies, or has found online.
- Teenagers may want to participate in decisions about their treatment. Include them in discussions with members of the healthcare team, as appropriate.
- You may need to discuss fertility preservation with your teenager. Some cancer treatments can affect fertility. Fertility preservation, such as egg or sperm banking, needs to be done before treatment begins. Enlist members of the healthcare team to help with this sensitive discussion.
- Teenagers maybe very concerned about changes to their physical appearance, such as hair loss and losing or gaining weight, as well as worrying about how their peers will react to the changes.
- As teenagers struggle to find independence, a cancer diagnosis may feel like a setback that can lead to feelings of frustration and anger. They may try to test their boundaries or engage in risky behaviors, such as drinking, drug use, or sex.

**Ways to Help Your Child Cope.** It will help your child cope with their diagnosis if you:

- Provide structure to increase your child's sense of control. Children crave structure in their environment. Make things as consistent as possible. For example, plan a regular routine that you will follow during your time together in the hospital or clinic.
- Acknowledge and praise your child when they are doing difficult things. Intermittent praise is the best way to reinforce the desirable behaviors that you want to see in your child.
- Use the same consequences for unacceptable or inappropriate behavior as you did before your child was diagnosed with cancer. Consistency will maintain structure and normalcy.
- Show that you respect your child's anger, worry, sadness or fear. Give them appropriate outlets for expressing these feelings, such as drawing or keeping a journal.
- Keep your child busy with activities during treatment to take their mind off difficult and unpleasant experiences.

- Help your child stay connected with friends from home and school with phone calls, texts and emails, or visits, if possible.
- Ask for professional assistance for your child if they are having an especially difficult time adjusting to the cancer diagnosis and its treatment.

**Siblings.** When a child is diagnosed with cancer, everyone in the family is affected by the experience. This includes their siblings, who may feel angry, anxious, lonely, sad, guilty, or even resentful of the new attention their sibling is receiving. You can help your other children cope with a sibling's diagnosis in some of the following ways:

- Give them the chance to talk about how the experience is affecting them.
- Be open and willing to answer questions about their brother's or sister's cancer and treatment.
- Reassure younger siblings that they cannot "catch" cancer from their brother or sister. Explain that their brother or sister did not do anything that caused the cancer.
- Let them know that their sibling with cancer may have less energy or lose their hair.
- Explain that other concerned family members and friends may ask them about their sibling's diagnosis. Talk about appropriate responses.
- Remember that brothers and sisters still have their own problems, unrelated to their sibling's cancer. Their problems are real and require your attention.
- Provide consistent, fair discipline to all your children, even though it may be more difficult right now.
- Let all your children know that you love them and are proud of them.

Siblings of children with cancer need to continue to go to school and participate in their usual activities, as much as possible. Ask friends, family, other parents, and teachers for help. However, disruptions to routines are inevitable, and the other children in your family may feel lost or overlooked. Arrange for regular "alone time" with each child.

Make sure the school is aware of the diagnosis. Talk to your other children's teachers. Ask your hospital's social worker or psychologist, or your school psychologist, whether your community offers any programs for siblings of children who have cancer. For additional assistance finding programs for siblings, you can also call an LLS Information Specialist at (800) 955-4572.

SuperSibs, a program of Alex's Lemonade Stand Foundation, provides programs and support for the siblings of children with cancer. Visit [www.alexslemonade.org/supersibs](http://www.alexslemonade.org/supersibs) to learn more.

**For additional support and information, please call an Information Specialist or visit [www.LLS.org/FamilyWorkbook](http://www.LLS.org/FamilyWorkbook) to find information for caregivers.**

# Treatment Planning

**Choosing a Hospital and Doctor for Your Child's Cancer Treatment.** Most children with cancer receive treatment at hospitals that specialize in treating children with cancer. The doctors and other healthcare providers at these centers have special training and expertise in giving comprehensive care to children. These centers are often members of the Children's Oncology Group (COG). This is the world's largest organization devoted to clinical research to improve the care and treatment of children with cancer.

Going to a specialized children's cancer hospital helps ensure that your child will get the best available treatment. You can ask your child's pediatrician or family doctor for a referral, or you can call an LLS Information Specialist at (800) 955-4572 to find hospitals that specialize in treating children with ALL.

Children who are diagnosed with ALL usually need to start treatment as soon as possible after diagnosis. Some families may wish to seek a second opinion, particularly if their child has a high-risk subtype of ALL, or if the ALL has come back (relapsed) after initial treatment. A second opinion may help you feel more confident about your child's treatment plan. The second opinion should come from a pediatric hematologist-oncologist, preferably one who specializes in childhood ALL. This doctor should have the most knowledge and experience regarding the latest treatment options.

Before you get a second opinion, you may want to check with your health insurance company to be sure that a second opinion will be covered by your plan. If you are unsure or feel uncomfortable about how to tell your child's doctor you are getting a second opinion, call an LLS Information Specialist to discuss a way that makes you feel comfortable.

**Fertility.** Some cancer treatments can affect your child's fertility (the ability to have children in the future). Before your child begins treatment, it is important to talk with the doctor about whether the treatment could affect your child's fertility. You may also want to speak with a fertility specialist, a doctor who diagnoses and treats problems related to infertility. This specialist can talk to you about possible options for preserving your child's fertility. However, delaying treatment to address fertility options may not always be recommended. Many children with ALL need to start treatment right away.

**For more information about fertility preservation, see the free LLS booklet *Fertility and Cancer*.**

**Pre-Treatment Testing.** Before your child starts treatment, the doctor will perform tests to learn more about your child's leukemia and overall health, and to find out if the leukemia has spread to other parts of the body. Doctors use this information for treatment planning. Some of these tests are summarized below.

**Blood Tests.** Doctors test blood to help plan treatment. Below are some blood tests used for treatment planning.

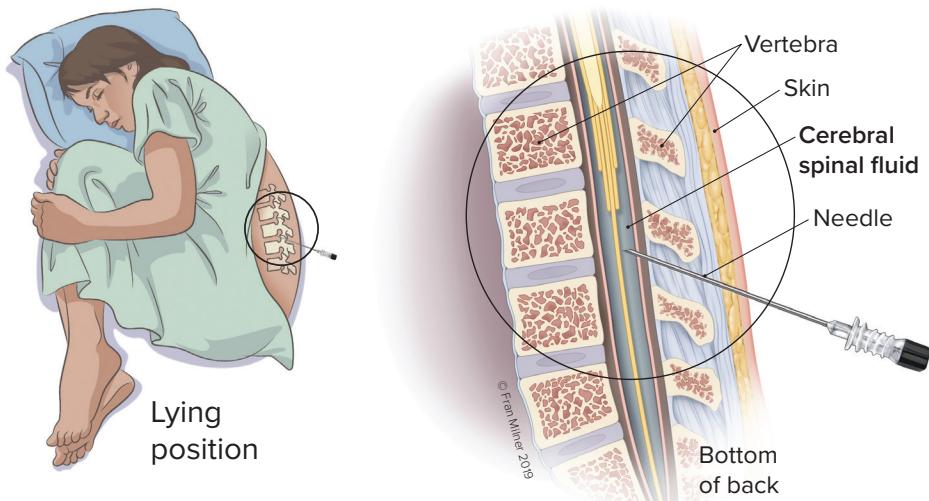
- **Complete Blood Count (CBC) with Differential.** This test is used to measure the number of red blood cells, white blood cells and platelets in a sample of blood. It also measures the amount of hemoglobin in the red blood cells. The CBC should include a differential, which measures the numbers of the different types of white blood cells in the sample.
- **Blood Chemistry Profile.** This blood test measures the levels of certain substances released into the blood by organs and tissues in the body. These substances include electrolytes (such as sodium, potassium and chloride), fats, proteins, glucose (blood sugar), uric acid and enzymes. Blood chemistry test findings indicate how well a person's kidneys, liver and other organs are working. A blood chemistry profile also provides helpful information about any potential organ damage caused by leukemia cells or ALL treatments.
- **Liver Function Tests.** The liver is the largest organ inside the body. It is located in the upper right side of the abdomen. It helps the body digest food, store energy and remove toxins from the blood. If leukemia cells are present in the liver, they can affect liver function. Some chemotherapy drugs can also damage the liver and affect liver function. Liver function tests are done to check how well the liver is working.
- **Coagulation Tests.** These tests measure the blood's ability to clot and stop bleeding. Certain proteins, called "coagulation factors," are needed for clotting. These proteins are made by the liver. In addition to checking how well the blood can clot, these tests can determine whether there are deficiencies in some proteins, such as the protein called fibrinogen. Coagulation tests can help assess your child's risk for excessive bleeding.
- **Tumor Lysis Syndrome (TLS) Panel.** Children with ALL may be at high risk for developing a condition called "tumor lysis syndrome (TLS)." This condition can occur after treatment begins, when a great many cancer cells may die within a short period of time. As the leukemia cells die, they break apart and release their contents into the bloodstream, which changes the normal balance of chemicals in the blood. This can overwhelm the kidneys because they cannot get rid of the toxic substances all at once. The effects of TLS can be life-threatening; they can be severe during the early phases of treatment, especially if white blood cell counts are very high before induction therapy. A TLS panel can help the doctor assess if your child is likely to get or already has TLS.
- **HLA Typing.** This consists of a blood test to identify certain proteins, called human leukocyte antigens (HLAs), found on the surface of most cells in the body. These proteins make up a person's tissue type, which varies from person to person. They also play an important role in the body's immune response to foreign substances by helping the body distinguish its own cells from foreign cells. HLA typing is done before allogeneic stem cell transplantation to find out if there is a tissue match between the donor

and the person receiving the transplant. It is an important test for newly diagnosed ALL patients, if allogeneic stem cell transplantation is being considered as a treatment option. For more information on allogeneic stem cell transplantation, see page 31.

**Lumbar Puncture.** ALL can spread to the fluid that flows around the brain and spinal cord, called the “cerebrospinal fluid.” In order to determine whether leukemia cells have spread to this area, a sample of the cerebrospinal fluid is tested in a procedure called a lumbar puncture or “spinal tap.”

After the area over the spine in the lower part of the back has been numbed with a local anesthetic, a thin needle is inserted between two bones in the spine (vertebrae) and into the cerebrospinal fluid. See **Figure 4** below. A sample of the fluid is withdrawn and examined under a microscope to look for leukemia cells that may have spread to the brain and spinal cord.

**Figure 4. Lumbar Puncture**



**Imaging Tests.** These tests create images (pictures) of the inside of the body. A radiologist is a doctor who specializes in reading these images. Various types of imaging tests are used to detect where a cancer is located in the body. Imaging tests are not routinely done for children with ALL, except in select circumstances.

- **Positron Emission Tomography-Computed Tomography (PET-CT) Scan.**

This procedure combines images from both a PET scan and a CT scan. The combined scans give a more detailed image of areas inside the body than either scan alone can. If lymphoblastic lymphoma is suspected, a whole-body PET/CT scan is recommended.

- **Ultrasound.** This imaging test uses high-energy sound waves to examine tissues and organs inside the body. For example, it can detect cancer in the testicles of males. If the testicles are not the same size or have any lumps, the doctor may order an ultrasound to see whether there is a mass in the testicles.
- **Echocardiogram.** Certain cancer treatments can damage the heart. The doctor may perform an echocardiogram as part of the treatment planning process to check how well the heart pumps blood. A computerized image of the heart is created by bouncing ultrasound waves off internal tissues or organs in the chest. An echocardiogram shows the size, shape and position of the heart, as well as its internal structures. It also shows if the heart is beating and pumping blood normally.

**See the free LLS book *Understanding Lab and Imaging Tests* for more information about these tests. Visit [www.LLS.org/3D](http://www.LLS.org/3D) to view interactive 3D illustrations of some lab and imaging tests.**

**Prognostic Factors.** Certain factors can affect a patient's prognosis—the probable outcome of a disease or ailment. Doctors use prognostic factors to help predict how likely a patient's disease is to respond to treatment. These factors help doctors plan the most appropriate treatment regimen for each patient.

They also help doctors determine which patients need more intense treatment. Some prognostic factors are called “favorable risk factors” because they are associated with a lower risk of disease relapse after treatment. Others are called “unfavorable risk factors” because they are associated with a higher risk of disease relapse after treatment.

Children with ALL are often categorized into one of three risk groups — standard risk, high risk, or very high risk — based on prognostic factors. This is called risk stratification. Typically, children with ALL in the low-risk group have a better prognosis and receive less intensive treatment than those in the two higher-risk groups.

Prognostic factors for children with ALL include:

- Age: ALL tends to be more aggressive in infants younger than 1 year and children older than 10 years.
- White blood cell count: Children with white blood cell counts of  $50 \times 10^9$  L or greater at the time of diagnosis need stronger treatment.
- Genetic factors: Certain changes in the chromosomes or genes can make the leukemia cells either easier or harder to treat. These changes help determine whether your child may benefit from treatment with more intensive therapies. See **Table 4** on page 26 that lists some of the genetic risk groups for children with B-cell ALL.

- Central nervous system involvement: Children with ALL who have leukemia cells in the central nervous system at diagnosis are at a higher risk of disease relapse.
- Treatment response: Children who have a better response to the initial induction therapy have a lower risk of disease relapse. For children with T-cell ALL, risk stratification is primarily based on their early treatment response.

**Table 4. Genetic Risk Groups for B-cell ALL**

Risk Groups	Genetics
Favorable risk features	<ul style="list-style-type: none"> <li>• High hyperdiploidy (51-67 chromosomes)           <ul style="list-style-type: none"> <li>▶ Trisomy of chromosomes 4, 10, and 17 are among trisomies that have the most favorable outcome</li> </ul> </li> <li>• Cryptic t(12;21)(p13;q22): <i>ETV6-RUNX1</i> fusion</li> </ul>
Unfavorable risk features	<ul style="list-style-type: none"> <li>• Hypodiploidy (&lt;44 chromosomes)</li> <li>• <i>KMT2Ar</i> (t[4;11] or others)</li> <li>• t(9;22)(q34;q11.2): <i>BCR-ABL1</i></li> <li>• <i>BCR-ABL1</i>-like (Ph-like) ALL           <ul style="list-style-type: none"> <li>▶ JAK-STAT (<i>CRLF2r</i>, <i>EPORr</i>, <i>JAK1/2/3r</i>, <i>TYK2r</i>, mutations of <i>SH2B3</i>, <i>IL7R</i>, <i>JAK1/2/3</i>)</li> <li>▶ ABL class (rearrangements of <i>ABL1</i>, <i>ABL2</i>, <i>PDGFRA</i>, <i>PDGFRB</i>, <i>FGFR</i>)</li> <li>▶ Other (<i>NTRKr</i>, <i>FLT3r</i>, <i>LYNr</i>, <i>PTK2Br</i>)</li> </ul> </li> <li>• t(17;19): <i>TCF3-HLF</i> fusion</li> <li>• Intrachromosomal amplification of chromosome 21 (<i>iAMP21</i>)</li> <li>• Alterations of <i>IKZF1</i></li> </ul>

Adapted from National Comprehensive Care Network, NCCN Clinical Practice Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia; 2021.

**Risk Groups for B-cell ALL.** Your doctor may describe your child's ALL in terms of its risk group. Patients are assigned to a risk group based on age, genetic and clinical features of the disease, and the results of laboratory tests.

Knowing your child's risk group helps the doctors develop the most effective treatment plan for your child. Patients with lower-risk ALL are more likely to have a favorable outcome and need less aggressive treatment. Children in the high-risk and very high-risk groups usually receive more intense treatment than children in the lower-risk groups.

Different institutions use different combinations of prognostic factors to assign patients into risk groups. The National Cancer Institute uses the following factors at diagnosis to assign children to risk groups:

**Standard (Low) Risk:** Children at least age 1 year and younger than 10 years who have a white blood cell count less than 50,000/ $\mu$ L at the time of diagnosis.

**High Risk:** Children 10 years and older and/or children who have a white blood count of 50,000/ $\mu$ L or more at the time of diagnosis.

**Very High Risk:** Children younger than age 1 year; children with certain genetic changes; children who have a slow response to initial treatment; children who have signs of leukemia after the first 4 weeks of treatment; and children with minimal residual disease after four weeks of induction therapy.

**Risk Groups for T-cell ALL.** For children with T-cell ALL, risk stratification is primarily based on how they respond to induction therapy (the first phase of treatment). Children who have a better response to the initial induction therapy have a lower risk of disease relapse.

## Treatment Options

New treatments may have been approved since this book was printed.  
Check [www.LLS.org/DrugUpdates](http://www.LLS.org/DrugUpdates) or call (800) 955-4572.

Before treatment begins, your child's doctor will discuss treatment options with you. Treatment options may include standard therapy or a clinical trial. "Standard therapy" is treatment that is accepted by medical experts as proper treatment for a certain type of disease. A "clinical trial" is a research study that tests how well a new medical treatment works in people. A clinical trial may be your child's best treatment option, so it is important to discuss all your child's treatment options with the doctor.

Not every child with ALL receives the same type of treatment. The doctor will tailor your child's treatment based on several factors, including the subtype of the disease. For example, children with ALL that has the Philadelphia chromosome are treated with a class of drugs called tyrosine kinase inhibitors (TKIs) in addition to chemotherapy.

### Talk to your doctor about

- Your child's treatment options and the results you can expect from treatment
- The results you can expect from standard treatment
- The possibility of your child participating in a clinical trial

**Administration of Therapies.** Treatments are given in different ways, including:

- Intravenous treatment. During an intravenous (IV) infusion, the drugs are injected slowly into a vein over the course of several minutes, a few hours, or even several days (in the case of a continuous infusion). Often, doctors give IV treatment through a thin, soft tube called a central venous line (also called a central line or catheter), which is placed in a large blood vessel in

the neck, chest or arm. When a patient has a central line in place, the drugs are administered through the line and doctors do not have to inject a needle into the patient's vein each time a treatment is administered. Doctors can also use the central line to give other medications and take blood samples. A central line can be left in place for weeks or months but must be carefully cleaned and maintained to minimize the risk of infections entering the bloodstream.

- Intramuscular injection. This treatment uses a needle to put medicine deep into the muscle. Patients may get an intramuscular injection in an arm or a leg.
- Oral treatment. Oral medications are taken by mouth and come in a variety of forms, including pills, capsules and liquids. It is important to always follow directions carefully for oral medications, including the need for special handling (gloves), storage (room temperature or refrigerated) and disposal. Keeping a diary to track oral medication may be helpful.
- Intrathecal treatment. This is treatment in which medicine is injected in the fluid-filled space that surrounds the brain and spinal cord, called the cerebrospinal fluid. This method of treatment may be used to kill any leukemia cells that might have spread to the brain or spinal cord. See *Central Nervous System (CNS) Prophylaxis* on page 33.
- Subcutaneous injection. With subcutaneous injection, the needle goes under the skin into the space between the skin and muscle, but does not enter the muscle.

**Types of Treatment.** Your child's treatment may include chemotherapy, targeted therapy, immunotherapy, radiation therapy, stem cell transplantation and/or CAR T-cell therapy. These treatments may be given in a hospital (inpatient treatment) or clinic (outpatient treatment).

**Chemotherapy.** The current standard treatment for ALL is long-term chemotherapy. It typically lasts for about 2 years, and it is often intense, especially in the first few months of treatment. The most common treatment regimens use a combination of more than one chemotherapy drug.

Chemotherapy drugs kill fast-growing cells throughout the body, including both cancer cells and normal, healthy cells. Different types of chemotherapy drugs work in different ways to eliminate leukemia cells or stop new leukemia cells from forming. As a result, more than one chemotherapy drug is usually used.

Chemotherapy is typically given in cycles. Each cycle is made up of a certain number of days of treatment, followed by a certain number of days of rest. The rest days allow the body time to recover before the next treatment cycle begins. Cycles vary in length, depending on which drugs are used.

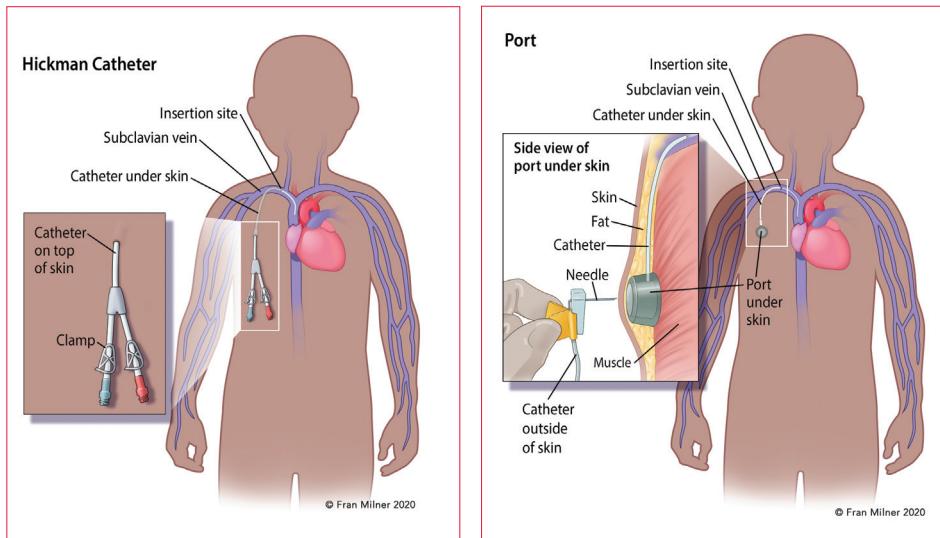
Some chemotherapy drugs are injected into a vein using a "catheter" or a "central line." A catheter is used to give chemotherapy and other drugs, blood

transfusions, and fluids directly into your child's bloodstream. They can also be used to remove blood for testing.

The central line is usually attached to a "port" that is surgically placed under the skin into the patient's upper chest, to allow access to the central line. Your child may be given general anesthesia or placed under "conscious sedation" during the procedure. Conscious sedation is a combination of medicines to help your child relax and to block pain during a medical procedure. Your child may appear to be asleep but wakes when spoken to or touched.

The port and central line can stay in place for months. **Figure 5** below illustrates a commonly used catheter and port called the Hickman®.

**Figure 5. Methods of Intravenous (IV) Injection: Hickman® Catheter and Port**



**Hickman® Catheter:** An example of a type of central line.

**Port:** A port used with a central line.

**Radiation Therapy.** Radiation therapy, also known as "radiotherapy," uses high-energy x-rays or other types of radiation to kill cancer cells in a small, targeted area of the body. Since radiation can also harm normal cells, whenever possible, radiation therapy is directed only at the affected areas where the cancer is, to reduce long-term side effects.

Radiation therapy may be used to treat ALL that has spread to the central nervous system (brain and spinal cord) or testicles. It may also be used to prepare the bone marrow for a stem cell transplantation.

**Targeted Therapy.** Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Not all cancers have the same targets. Each type of targeted therapy works a little bit differently, but they all interfere with the growth

and survival of cancer cells. To find the most effective treatment, your doctor may run tests to identify the genes, proteins and other factors in your cancer cells. This helps the doctor choose the most effective treatment for you based on the specific factors of your disease. Targeted therapy may be used alone or in combination with chemotherapy. Some types of targeted therapy include:

**Tyrosine Kinase Inhibitors (TKIs).** Tyrosine kinases are enzymes that are a part of many cell functions including cell signaling, growth and division. These enzymes may become too active in patients with an ALL subtype called Philadelphia chromosome-positive ALL (called Ph+ ALL). For more information on Ph+ ALL, see page 37.

Tyrosine kinase inhibitors (TKIs) work to block these overactive enzymes and may stop cancer cells from growing. TKIs are pills taken by mouth. They are generally not used alone to treat ALL. Instead, they are added to a combination chemotherapy regimen.

The following TKIs have been approved to treat Ph+ ALL in children:

- **Imatinib (Gleevec®)**
- **Dasatinib (Sprycel®)**

See *Drugs Used in the Treatment of ALL* starting on page 56.

Common side effects of TKIs include low blood counts, abnormal bleeding, nausea and vomiting, diarrhea, fatigue, rashes, headaches, and pain in muscles, bones and joints. TKIs may also cause fluid to collect under the eyes and in the hands, feet or lungs. Uncommon but serious side effects include heart rhythm changes, blood vessel narrowing or blood clot formation. Dasatinib may cause fluid to collect around the lungs.

**Monoclonal Antibodies.** Monoclonal antibodies are proteins that are made in a laboratory. They can bind to substances in the body, including cancer cells. Most are designed to attach to one specific substance. These drugs can be used alone to destroy cancer cells or to carry drugs, toxins or radioactive substances directly to the cancer cells.

Monoclonal antibodies target antigens (proteins) on the surface of leukemia cells; these are called cluster of differentiation (CD) antigens. B-cell ALL is characterized by the presence of proteins CD10, CD19, CD20, CD22, CD24, and CD79a. On the other hand, T-cell ALL is typically associated with the presence of CD3.

- **Blinatumomab (Blincyto®)** is a “bispecific” antibody, a type of antibody that can bind to two different antigens at the same time.

Blinatumomab is a liquid administered slowly through a vein by IV as a continuous infusion over a period of 28 days. Hospitalization is typically recommended for the first few days of treatment. Side effects of blinatumomab may include fever, headache, infection, nausea, diarrhea and neurological complications such as seizures, confusion, slurred speech and loss of balance.

- **Inotuzumab ozogamicin (Besponsa®)** is a monoclonal antibody linked to a chemotherapy drug. Studies of inotuzumab ozogamicin in children are ongoing. Inotuzumab ozogamicin targets CD22, a cell surface antigen expressed on the cancer cells of most B-cell ALL patients. When inotuzumab ozogamicin binds to the CD22 antigen on B cells, it enters the cell and then releases the chemotherapy drug calicheamicin, causing the cell to die.

See *Drugs Used in the Treatment of ALL* starting on page 56.

**Chimeric Antigen Receptor (CAR) T-Cell Therapy.** CAR T-cell therapy is a type of immunotherapy that consists of engineering a patient's own immune cells to recognize and attack cancer cells. The T cells are removed from the patient's body and then genetically engineered in a laboratory to produce receptors on their surfaces called "chimeric antigen receptors" (CARs). These receptors recognize and bind to a specific target found on the cancer cells. The most frequently targeted antigen in CAR T-cell immunotherapy for leukemia is called "cluster of differentiation 19" (CD19). The CD19 antigen is expressed on the surfaces of nearly all healthy and cancerous B cells, including leukemia B cells.

**Tisagenlecleucel (Kymriah®)** is designed to help the body's own immune system fight cancer. Each dose is made for a specific patient, using the patient's own T cells (white blood cells that help the body fight infections and cancer). The T cells are collected from the patient and then genetically modified to add a new gene containing a CAR protein, so that these new CAR T cells can identify and kill leukemia cells with CD19 on their surfaces. These modified cells are infused back into the patient's bloodstream to kill the cancer cells.

While CAR T-cell therapy can be an effective treatment, it is also associated with a relatively high rate of serious complications such as high fever, low blood pressure, breathing difficulties, delirium, aphasia (loss of ability to speak and understand language) and neurologic complications. As a result, it can only be given at specialized centers that have expertise in delivering this type of treatment.

See *Drugs Used in the Treatment of ALL* starting on page 56.

**For more comprehensive information, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see and download the free LLS booklet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts*. Visit [www.LLS.org/TreatmentVideos](http://www.LLS.org/TreatmentVideos) for child-friendly videos about CAR T-cell therapy.**

**Allogeneic Stem Cell Transplantation.** Some patients with ALL may benefit from stem cell transplantation. However, stem cell transplantation is not used as the first or primary treatment for children with ALL. It may be used as a treatment for high-risk children who have ALL, or for children who have not responded to any other treatments. The goal of stem cell transplantation is to cure the patient's cancer by first destroying the cancer cells in the bone marrow with high doses of chemotherapy, with or without radiation therapy. Such high doses of chemotherapy, however, can damage the stem cells in the bone marrow,

resulting in life-threatening anemia, infections and uncontrolled bleeding. After the chemotherapy, the patient receives an infusion of healthy stem cells from a donor to replace those destroyed by the intensive chemotherapy. The healthy blood stem cells then grow and multiply, forming new bone marrow and blood cells.

An allogeneic stem cell transplantation creates a new immune system for the patient that helps the body fight infections and other diseases. The new immune system also has the potential to recognize and attack any remaining cancer cells in the body. The transplanted immune cells (called the “graft”) identify the leukemia cells in the body as foreign and destroy them. This is called the “graft-versus-leukemia (GVL) effect.”

Unfortunately, sometimes a very serious side effect, called graft-versus-host disease (GVHD), can develop after transplantation of the stem cells. GVHD occurs when the transplanted donor immune cells (the graft) identify the cells in the recipient’s body (the host) as foreign and attack them. The parts of the body that are most commonly damaged by GVHD include the skin, liver, stomach, intestines and eyes. GVHD can develop within weeks after transplantation or much later. Doctors can prescribe medication to help prevent or minimize the complications of GVHD.

#### **Talk to your doctor about**

- Stem cell transplantation and ask whether it is a treatment option for your child

**For further information about all types of stem cell transplantation, see the free LLS books *Blood and Marrow Stem Cell Transplantation* and *Cord Blood Stem Cell Transplantation*.**

**Phases of Treatment.** The goal of treatment is to kill the leukemia cells and stop the bone marrow from making any more leukemia cells. The main treatment for ALL is chemotherapy that is divided into phases. Each phase differs in length and the type of medicines that are used. Some treatment plans may also include targeted agents or, possibly, stem cell transplantation.

Treatment regimens for ALL include central nervous system (CNS) prophylaxis to prevent leukemia cells from spreading to the area around the brain and spinal cord. CNS prophylaxis is typically given to children throughout all phases of ALL treatment. For more information about CNS prophylaxis, see page 33.

**Induction Therapy.** The first phase of chemotherapy is called “induction therapy.” The goal of induction therapy is to destroy as many cancer cells as possible to induce (achieve) a remission.

Induction therapy lasts for 4 weeks. The specific drugs, dosages and timing of administration depend on several factors, including the patient’s age and the specific features of the leukemia cells.

Your child may spend some or most of this time in the hospital during this phase of treatment, depending on your child's clinical condition. For some children, the hospital stay is the first time they have been away from home for an extended period of time. Most hospitals allow a parent to stay at the child's bedside during hospitalization.

Providing age-appropriate information about the illness and its treatment will help your child build trust in you and the members of the treatment team. Talking with your child about his or her fears and concerns will also help your child feel more comfortable.

**For practical guidance about how to support your child and other family members, deal with your own concerns and share news with extended family and friends, visit [www.LLS.org/FamilyWorkbook](http://www.LLS.org/FamilyWorkbook) for the *Caring for Kids and Adolescents with Blood Cancer* workbook.**

Children with standard-risk ALL often receive three drugs for the first month of treatment. These include the chemotherapy drugs **vincristine** and **pegaspargase** and the corticosteroid **dexamethasone**. For children in the high-risk groups, another chemotherapy drug in the anthracycline family, such as **daunorubicin** or **doxorubicin**, is typically added. Older children may receive the corticosteroid **prednisone** instead of dexamethasone.

In addition to the treatment(s) above, children with Philadelphia chromosome-positive (Ph+) ALL and Philadelphia chromosome-like (Ph-like) ALL are also given a tyrosine kinase inhibitor (TKI) medication, such as **imatinib (Gleevec®)** or **dasatinib (Sprycel®)**. Some children with Ph-like ALL may be treated with a TKI called **ruxolitinib (Jakafi®)**, usually in a clinical trial. See page 37 for more information on special treatment considerations for children with Ph+ ALL and Ph-like ALL.

**Central Nervous System (CNS) Prophylaxis.** Pediatric regimens typically include treatment to prevent the spread of leukemia cells to the central nervous system and to kill any leukemia cells that may already be present in the brain and spinal cord. It is uncommon for leukemia cells to be present in the cerebrospinal fluid at the time of diagnosis; this occurs in only 3 to 7 percent of cases. However, without the routine treatment targeting the central nervous system (referred to as "CNS prophylaxis"), leukemia cells will eventually spread to the cerebrospinal fluid in a large percentage of patients (50 percent or more). The CNS-directed therapy is typically given to all patients throughout the entire course of ALL treatment. It begins during the induction phase and continues throughout the rest of the treatment regimen.

Central nervous system-directed—therapy may include:

- **Intrathecal chemotherapy**, in which anti-cancer drugs are injected into the fluid-filled space between the thin layers of tissue that cover the brain

and spinal cord. The most common intrathecal chemotherapy drug used in children with ALL is **methotrexate**. Sometimes, other drugs such as **cytarabine** and a corticosteroid are used, particularly in children with high-risk ALL.

- **Systemic chemotherapy**, in which anti-cancer drugs are injected into a vein and travel through the blood to cells throughout the body. **High-dose methotrexate** is the most common drug used for this treatment in children with high-risk B-cell ALL. **Dexamethasone**, **cytarabine** and **pegaspargase** may also be included.
- **Cranial irradiation**, in which radiation therapy to the brain is used to kill cancer cells. Cranial radiation is no longer routinely used in children with ALL, except in those with leukemia cells in their cerebrospinal fluid at the time of diagnosis or those with CNS relapse. Cranial radiation is almost never used in very young children. Radiation therapy can increase a child's risk of developing long-term and late effects, such as problems with thinking, growth and development. However, it is very effective in the treatment of CNS leukemia, when indicated.

**Assessing Treatment Response.** At the end of the month of induction therapy, your child will have another bone marrow aspiration performed. The bone marrow sample is examined under a microscope. (Children with acute lymphoblastic lymphoma may not need a bone marrow test and may instead require imaging studies only; see page 5 for information about acute lymphoblastic lymphoma.) These tests or imaging studies are to check whether your child's leukemia or lymphoma is in complete remission. A complete remission is achieved when:

- No more than 5 percent of cells in the bone marrow are blast cells
- No blasts are in the bloodstream
- Blood cell counts are back to normal
- All signs and symptoms of ALL are gone

Over 95 percent of children achieve a remission at the end of induction therapy. However, remission does not mean that your child is cured. Your child still needs more treatment to ensure that the disease does not relapse (come back).

**Minimal/Measurable Residual Disease (MRD).** Even when a complete remission is achieved, some leukemia cells that cannot be seen with a microscope may remain in the body. The presence of these cells is referred to as minimal or measurable residual disease (MRD). Patients who have achieved remission after initial treatment but have MRD are at increased risk of disease relapse. Testing for MRD can help your child's doctor re-evaluate your child's ALL risk category and determine whether your child may benefit from further intensified therapies.

It is important for your child to get tested for MRD even after achieving remission. There are very sensitive tests to detect MRD. The most widely used tests are flow cytometry, polymerase chain reaction (PCR) and next-generation sequencing. These tests use samples of bone marrow cells.

Routinely, MRD testing is done after the completion of induction therapy. Recommendations for additional MRD testing depend on the treatment regimen used.

If your child tests negative for MRD, that indicates that the tests did not detect residual leukemia cells. If your child tests positive for MRD, there are still detectable leukemia cells inside the bone marrow. Children who are MRD-positive after induction therapy are categorized as having high-risk or very high-risk ALL. Depending on the amount of MRD, your child's doctor may change the treatment plan. Your child may undergo more intense treatment.

If your child is in remission but tests positive for MRD, the doctor may prescribe a drug called **blinatumomab (Blincyto®)**.

See *Drugs Used in the Treatment of ALL* starting on page 56.

For patients who do not achieve remission after the first course of induction chemotherapy, a second course of chemotherapy is given, usually using different chemotherapy drugs.

**See the free LLS fact sheet *Minimal/Measurable Residual Disease (MRD) for more information.***

Children with leukemia cells in their testicles at diagnosis—that is not resolved by the end of induction therapy—may receive radiation treatment to the testicles.

**Postremission Therapy.** “Postremission therapy” refers to treatment given to patients after their disease is in complete remission. Even when MRD test results are negative, undetectable residual cancer cells are believed to remain in the body. Because of this, patients with ALL require additional phases of treatment after they achieve remission. Most of these phases are given in an outpatient setting, while some phases require a brief hospitalization for chemotherapy administration. During this period, children also continue to receive CNS prophylaxis therapy.

**Consolidation Therapy.** Consolidation therapy, also called “intensification,” begins after induction therapy. The goal of consolidation therapy is to kill any remaining leukemia cells in the body that may cause a relapse. In this phase of treatment, lower-risk patients typically receive less intensive therapy, while higher-risk patients receive therapy that is more intense.

The consolidation phase usually lasts for a period of 4 to 8 weeks, depending on the ALL risk category and treatment protocol. Consolidation chemotherapy does not usually require a hospital stay. It is often given in an outpatient setting, allowing your child to go home after each scheduled treatment. But if there are complications, such as fever or infection, a child may be admitted to the hospital.

The combination of drugs and the duration of therapy for consolidation regimens vary, but can consist of combinations of drugs like those used during the induction phase. Generally, several chemotherapy drugs are combined to help prevent the leukemia cells from developing drug resistance.

Some of the drugs frequently incorporated into consolidation regimens include:

- **Cytarabine**
- **Vincristine**
- **6-mercaptopurine (6-MP)**
- **Cyclophosphamide**
- **Pegasparagase**
- Intrathecal chemotherapy (to prevent the spread of ALL to the central nervous system)

See *Drugs Used in the Treatment of ALL* starting on page 56.

**Interim Maintenance.** After consolidation therapy, there is a recovery period called “interim maintenance.” Interim maintenance is typically given for up to 8 weeks, depending on your child’s treatment plan. This phase aims to maintain the remission, but also allows the bone marrow to recover from the effects of therapy. Interim maintenance typically involves chemotherapy that does not cause decreased blood cell counts. Patients receive **methotrexate** in combination with other chemotherapy agents. Methotrexate is given intravenously. If lower doses are prescribed, it may be given in a clinic. Higher doses may require a stay of 2 to 3 days in the hospital.

**Delayed Intensification.** The goal of the delayed intensification phase of treatment is to eliminate residual, drug-resistant leukemia cells from the body. It typically lasts 8 weeks and includes chemotherapy combinations like those used in the induction and consolidation phases. The exact timing of the doses and the specific drugs given will depend on the individual characteristics of your child’s disease. Some of the drugs that are frequently incorporated into delayed intensification regimens include:

- **Vincristine**
- **Dexamethasone**
- **Pegasparagase**
- **Doxorubicin**
- **6-thioguanine**
- **Cyclophosphamide**
- **Cytarabine**
- Intrathecal chemotherapy (to prevent the spread of ALL to the central nervous system (CNS))

Delayed intensification does not usually require a hospital stay, but children are sometimes admitted to the hospital for complications, such as fever and infection.

**Maintenance.** Maintenance is the last and longest phase of treatment. The goal of maintenance therapy is to prevent disease relapse. Children receive lower doses of chemotherapy during the maintenance phase and, as a result, tend to have less-severe side effects. Maintenance therapy usually lasts until 2 years from the start of interim maintenance. Most maintenance regimens include:

- **Oral 6-mercaptopurine** (administered daily) by mouth
- **Oral methotrexate** (administered weekly) by mouth
- Periodic doses of **vincristine** given as an IV injection and corticosteroids (**prednisone, dexamethasone**) by mouth
- Intrathecal chemotherapy (to prevent the spread of ALL to the central nervous system)

See *Drugs Used in the Treatment of ALL* starting on page 56.

Because some of these medications are taken orally at home, it is extremely important that a parent or caretaker ensure that the child takes the medication as prescribed by the doctor. Not taking the medication as prescribed by the doctor can increase the chance that the cancer will come back.

## Special Treatment Considerations

### Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL).

About 2 to 4 percent of children with ALL have a subtype called Philadelphia chromosome-positive ALL (also known as “Ph+ ALL” or “Ph-positive ALL”). The leukemia cells of these patients have the Philadelphia chromosome, which is formed by a translocation between parts of chromosomes 9 and 22. A piece of chromosome 9 breaks off and attaches to chromosome 22, and a piece of chromosome 22 similarly breaks off and attaches to chromosome 9. The new, abnormal chromosome 22 is known as the Philadelphia chromosome. This chromosomal alteration creates a gene called *BCR-ABL1*. This gene produces a protein called a tyrosine kinase, which causes the leukemia cells to grow and divide out of control.

Patients who have Ph+ ALL are typically treated with tyrosine kinase inhibitors (TKIs) combined with chemotherapy. This combination has become the standard of care for Ph+ ALL patients. New combinations of drugs for the treatment of Ph+ ALL are also being studied in clinical trials. See *Tyrosine Kinase Inhibitors* on page 30 for more information about TKIs.

**Philadelphia Chromosome-like (Ph-like) ALL.** About 15 percent of children with ALL have a subtype of B-cell ALL called “Ph-like ALL.” This is a high-risk subtype

of ALL in children that seems to peak in adolescents and young adults and is more likely to be seen in males. It is associated with an unfavorable prognosis.

Ph-like ALL has genetic features similar to Ph+ ALL, but without the *BCR-ABL1* fusion gene that defines Ph+ ALL. Instead, patients have a highly diverse range of genetic mutations that activate tyrosine kinase signaling. Tyrosine kinases are enzymes that play a part in many cell functions, including cell signaling, growth and division. These enzymes may be too active in leukemia cells. Tyrosine kinase inhibitors (TKIs) are drugs that work by blocking enzyme activity in a way that may prevent cancer cells from growing. Recent studies that analyzed the genetic profile of patients with Ph-like ALL have suggested that using TKIs and other targeted therapies may help treat these leukemias. This is an area of active clinical research.

**T-Cell ALL.** This is an aggressive cancer that has historically been associated with a poor prognosis. However, the development of intensive treatment regimens focused on T-cell ALL has led to significant improvements for children with this type of the disease. Treatment outcomes for children with T-cell ALL are now nearly equivalent to those of children with B-cell ALL.

Early intensification of therapy improves outcomes in patients with T-cell ALL. Patients typically receive early intensified induction therapy with a regimen of four drugs containing **vincristine, pegaspargase**, an anthracycline (such as **daunorubicin** or **doxorubicin**) and a corticosteroid (such as **dexamethasone** or **prednisone**), followed by an intensive consolidation regimen.

For relapsed and refractory patients, **nelarabine (Arranon®)** is an approved treatment. Most children with T-cell ALL do not need an allogeneic stem cell transplant to be cured. Still, a transplant may be recommended for children who have a high level of minimal residual disease (MRD) at the end of consolidation therapy. See page 31 for more information on allogeneic stem cell transplantation.

See *Drugs Used in the Treatment of ALL* starting on page 56.

**Infant ALL.** Infant ALL generally refers to cases of ALL diagnosed in children younger than age 1. Leukemia is very rare in infants. There are only approximately 90 cases of infant ALL per year in the United States.

Most infants with ALL have aggressive features, including high white blood cell counts, central nervous system involvement and presence of leukemia cells in the skin (a condition called “leukemia cutis”).

About 70 percent to 80 percent of infants with ALL have a chromosomal abnormality that involves the rearrangement in the *KMT2A* gene. These *KMT2A* rearrangements are associated with poor outcomes. As a result, infant patients typically need to be treated with intensive chemotherapy regimens. However, infants are very vulnerable to treatment-related toxicities and newer, less-toxic treatments continue to be studied in clinical trials.

Treatment of infant ALL is generally different from the treatment for older children with ALL. A series of clinical trials called “Interfant” have studied results of different regimens in infants vs children. Infants are today often treated with Interfant-based chemotherapy. Interfant induction is a multi-drug regimen that may include:

- **Prednisone**
- **Dexamethasone**
- **Vincristine**
- **Cytarabine**
- **Cyclophosphamide**
- **Daunorubicin**
- **Pegasparagase**
- **Methotrexate**

See *Drugs Used in the Treatment of ALL* starting on page 56.

Treatment regimens also include CNS prophylaxis. For more information on CNS prophylaxis see page 33.

After induction, your child’s treatment will be based on whether their leukemia cells have a rearrangement of the *KMT2A* gene. Infants are placed in risk groups based on their *KMT2A* status. See **Table 5** below, for definition of infant risk groups.

**Table 5. Infant Risk Group Definitions**

Risk Group	Features
High	<i>KMT2A</i> -rearranged; <b>and</b> Age < 3 months with any WBC or age <6 months with WBC $\geq$ 300,000; or Remains MRD+ after intensive consolidation therapy (any age/WBC)
Intermediate	<i>KMT2A</i> -rearranged and not high risk
Standard	<i>KMT2A</i> not rearranged

Adapted from National Comprehensive Care Network, NCCN Clinical Practice Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia; 2021.

For intermediate-risk and standard-risk patients, multi-drug chemotherapy may be a treatment option. For infants in the high-risk group, allogeneic stem cell transplantation or multi-drug chemotherapy may be considered as treatment options. For more information on allogeneic stem cell transplantation, see page 31.

Clinical trials are underway to study new treatments designed to improve cure rates in infants. Patients and caregivers can work with LLS Clinical Trial Nurse Navigators to help find potential clinical trials for infants.

**Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) to work with Clinical Trial Nurse Navigators to helps search for clinical trials for infants with ALL.**

**Older Adolescents and Young Adults (AYA).** The term “AYA population” generally refers to patients aged 15 to 39 years. Historically, the AYA population has been treated with either a pediatric ALL regimen or an adult ALL regimen, depending on the treatment center’s protocol for this age group. Adult treatment regimens and pediatric treatment regimens differ in the following ways:

- Pediatric regimens are more intense and complex than those given to adults. Adults typically receive lower doses of chemotherapy.
- Pediatric regimens tend to use more **pegaspargase**, **vincristine** and **corticosteroids**. In contrast, adult regimens tend to use more **cyclophosphamide** and anthracyclines, such as **doxorubicin** and **daunorubicin**.
- Pediatric treatments are given for longer periods of time than adult regimens. Central nervous system treatment (CNS prophylaxis) is started earlier and given for a longer time. See page 33.
- Adult protocols also entail a greater use of allogeneic stem cell transplantation compared to pediatric protocols. See page 31.

In clinical trials, researchers have started looking into the use of a variety of pediatric protocol options for older adolescent and young adult patients. They have found that AYA patients treated with pediatric protocols have achieved superior outcomes including better rates of survival compared to AYA patients treated with adult ALL protocols.

**Down Syndrome.** Down syndrome occurs in people who have an extra copy of chromosome 21, also called “trisomy 21.” Children with Down syndrome have an increased risk of developing ALL during childhood compared to children without Down syndrome.

Historically, children with ALL and Down syndrome have been shown to have poorer outcomes compared with children who have ALL but who do not have Down syndrome. Children with Down syndrome have an increased sensitivity to chemotherapy and are more likely to suffer complications from chemotherapy due to the side effects of treatment. Additionally, some studies have suggested that children with Down syndrome may have a higher chance of ALL relapse.

Children with Down syndrome who have ALL require special attention. They particularly need treatment protocols that are not only effective but less toxic than traditional treatments used for childhood ALL. These children can benefit from being treated at a major children’s hospital where the doctors have experience treating other Down syndrome children and are aware of the special care they require.

# Treatment for Relapsed and Refractory Disease

Most children with ALL are cured with standard chemotherapy treatments. But about 15 percent of young patients have ALL that returns after remission. This is referred to as a “relapse” of the disease (or “relapsed ALL”). Some children are unable to achieve a remission because their cancer does not respond to treatment. In these cases, the disease is referred to as “refractory” (or “refractory ALL”).

Relapsed/refractory disease is very serious and can be more difficult to treat. But there are treatment options available. Treatment for relapsed or refractory ALL is usually more intensive than the treatment used following initial diagnosis. It is important to understand all your child’s treatment options.

Before treatment, genetic testing of the leukemia cells is recommended for patients with relapsed or refractory disease. The mutational pattern of the leukemia cells may be different from when the disease was first diagnosed, and this can affect treatment decisions. For patients with Ph+ ALL, new mutations in the *BCR-ABL1* gene may occur over time. Some mutations can lead to resistance to certain TKIs. Before a patient starts treatment, *BCR-ABL1* mutation testing should be done to look for new mutations that may cause certain TKIs to stop working.

**Relapsed ALL.** The goal of treatment for relapsed ALL is to achieve a complete remission again and keep the leukemia from returning. The treatment your child needs depends on a number of factors including:

- The type of ALL (B-cell or T-cell)
- The location in the body the relapse has occurred. When the cancer returns in the bone marrow, it is called “isolated medullary relapse.” When the cancer occurs outside the bone marrow (for example in the central nervous system or testicles), it is called “isolated extramedullary relapse.”
- The amount of time that has passed between the initial diagnosis and detection of relapse. Recurrences that occur 3 years or more after diagnosis have a better prognosis.
- The results of genetic testing of the leukemia cells
- The prior treatments your child has received for ALL

**Refractory ALL.** The goal of treatment for refractory ALL is to try to attack the disease in a different way. Your child’s doctor will use different drugs or different combinations to attain a remission, and then use other therapies to increase the chances of a cure. The type of treatment will depend on:

- The type of ALL (B-cell or T-cell)
- The location in the body where the disease is persistent
- The results of genetic testing of the leukemia cells
- The prior treatments your child has received for ALL

**Treatment Options for Relapsed and Refractory ALL.** Treatments for relapsed/refractory ALL may include:

- A clinical trial
- New or different chemotherapy drugs or new combinations of chemotherapy drugs
- **Nelarabine** for patients with T-cell ALL
- **Blinatumomab (Blincyto®)**
- **Inotuzumab ozogamicin (Besponsa®)**
- Allogeneic stem cell transplantation for patients with an available donor
- CAR T-cell therapy

See *Drugs Used in the Treatment of ALL* starting on page 56.

#### **Talk to your doctor about**

- Therapies under study in clinical trials for refractory or relapse ALL

## **Clinical Trials for Blood Cancers**

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be used. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to

- Treat cancer using
  - A new drug
  - An approved drug to treat a different kind of cancer
  - A new combination of drugs
  - A new way of giving a drug (pill, intravenously (IV), etc

- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease, gain access to new, cutting-edge therapies, and provide helpful information for future patients. The treatments and information we have today are due in large part to patients being willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit [www.LLS.org/WhatToAsk](http://www.LLS.org/WhatToAsk) for lists of suggested questions).
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes.

Clinical trials can be difficult to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome the barriers to enrollment and provide support throughout the entire clinical trial process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (like past treatments, treatment responses, and your cancer genetic profile), your current health, and your medical history, because these might impact whether you can take part in certain clinical trials
- Help you understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical trial process

**Please call an LLS Information Specialist at (800) 955-4572 or visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information about clinical trials and the Clinical Trial Support Center at LLS.**

**Also, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to view *Understanding Clinical Trials for Blood Cancers*.**

## Related Disease

**Mixed Phenotype Acute Leukemia (MPAL).** Mixed phenotype acute leukemia (MPAL), also known as “biphenotypic leukemia” or “mixed lineage leukemia,” is a subtype of acute leukemia of ambiguous lineage. It is a combination of two forms of leukemia: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). It accounts for 2 to 5 percent of all acute leukemias, affecting patients of all ages, and includes several different subtypes.

The best treatment approach for MPAL has not yet been determined, and it is associated with a poor prognosis. This is due to the difficulty in correctly identifying this type of leukemia, its low incidence, the lack of experience in treating it, and its tendency to be resistant to both ALL and AML therapies. The reasons for this resistance are not yet clear, but it may be related to the high percentage of high-risk chromosomal abnormalities found in patients with MPAL. Currently there is no standard therapy for MPAL, but clinical trials are underway. Some studies have shown that ALL therapy may be the preferred approach.

A variety of factors are involved in determining the best treatment for patients with MPAL. These include the patient’s age, medical history (and other relevant medical conditions), and the characteristics of the leukemia cells as determined by immunophenotyping and genetic tests. It is also important to determine whether the patient has the Philadelphia chromosome-positive (Ph+) subtype, which accounts for about 25 percent of all cases of MPAL. Treatment for MPAL usually consists of a chemotherapy regimen for ALL, based on the patient’s age, in combination with a tyrosine kinase inhibitor (TKI). This is followed by allogeneic stem cell transplantation, if needed.

For patients with a Ph-negative subtype of MPAL, the treatment typically consists of either an ALL regimen, or a combination of ALL and AML therapies. This may be followed by an allogeneic stem cell transplantation when a donor is available.

**Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) to work with Clinical Trial Nurse Navigators to help search for clinical trials for patients with MPAL.**

## Side Effects and Complications

Side effects occur when treatment affects healthy tissue and organs. Most children with ALL are treated with intensive chemotherapy, which can cause severe side effects. Most side effects in children with ALL are temporary and subside once the body adjusts to therapy, or when therapy is completed. If side effects become severe, a child may need to be hospitalized.

**Low Blood Cell Counts.** Cancer and cancer treatments often cause drops in blood cell counts. This can result in a severe deficiency in the patient’s number of red blood cells, white blood cells and platelets.

For children with severe or prolonged low red blood cell and platelet counts, transfusions of red blood cells and platelets may be needed. Blood cell counts usually return to normal levels after the transfusion(s). Red blood cell and platelet transfusions are almost always needed for several weeks during treatment. After that, the blood cell counts usually return to normal levels.

During ALL treatment, the low white blood cell counts can lead to infections from bacteria and fungi that are normally present in the environment, on the skin, in the nose and mouth, on the gums or in the colon. The risk of infection may be increased because chemotherapy damages the cells lining the mouth and intestines, making it easier for bacteria to enter the bloodstream. When patients have a low white blood cell count, antibiotics are commonly given to prevent bacterial infection, and other drugs are given to prevent fungal and viral infections.

Because of the increased risk of infection during treatment, medical staff, family and friends need to practice frequent and vigorous handwashing and take other precautions to avoid exposing patients to bacteria, viruses and other infection-causing agents. Caregivers of children who have central lines or ports need to be meticulous when cleaning insertion sites and catheters, as instructed by their medical team.

Seek medical attention for your child immediately if any signs of infection develop at home. A temperature of 100.4°F or higher or the onset of chills may be the only sign of infection. Other signs of infection may include persistent coughing, sore throat, pain during urination, or diarrhea.

**Tumor Lysis Syndrome.** Children with ALL may be at risk for developing a condition called “tumor lysis syndrome” (TLS). This condition occurs when a large number of cancer cells die within a short period of time, releasing their contents into the blood. TLS can be severe during the early phases of treatment, especially for those children who have very high white blood cell counts before induction therapy.

Uric acid is one of the chemicals released by dying cancer cells. Very high levels of uric acid and other chemicals can cause severe damage to the kidneys and heart. If untreated, TLS can lead to heart arrhythmias, seizures, loss of muscle control, acute kidney failure and even death.

Treatment should include hydration to reduce the risk of developing TLS. Intravenous (IV) fluids are usually started at the time of diagnosis and are continued throughout chemotherapy to prevent chemical imbalances in the blood and to support kidney function. Children with ALL are constantly monitored for the development of TLS and are given drugs, such as **allopurinol (Zyloprim®)** or **rasburicase (Elitek®)**, to prevent or lessen the effects of TLS.

**Pain.** Bone pain may occur in children with ALL at the time of diagnosis or during a relapse, due to leukemia cells in the bone marrow. Rarely, some chemotherapy medicines used for patients with ALL can cause peripheral

neuropathy, a nerve problem that can cause pain, numbness and tingling usually in the hands or feet. Use of pain medications and physical therapy are very effective approaches for patients with pain from leukemia or leukemia treatment.

**Other Side Effects.** Chemotherapy drugs affect cells that divide quickly, which is why they work against cancer cells. But chemotherapy drugs also affect healthy cells in the body that divide quickly, such as the lining of the intestines, the skin, and hair follicles. Common side effects of chemotherapy may include:

- Hair loss
- Rashes
- Itchy skin
- Mouth sores
- Diarrhea
- Nausea and vomiting
- Headaches
- Loss of appetite
- Fatigue

These short-term side effects usually go away once a patient has completed treatment. Fortunately, drugs that counteract nausea and vomiting can be given to prevent or relieve this distressing side effect.

The use of corticosteroids, such as **prednisone** and **dexamethasone**, is a main component of virtually every induction therapy regimen for ALL. These drugs are also frequently incorporated into consolidation and maintenance therapy regimens. Acute side effects of corticosteroids may include weight gain, hyperglycemia (high blood sugar), corticosteroid-induced diabetes, and hypertension (high blood pressure). Patients should be monitored to ensure that their glucose (blood sugar) levels are under control. Gastric ulcers are another potential side effect of corticosteroid therapy. Medicines that reduce stomach acid, such as H2 blockers or proton-pump inhibitor drugs, may be recommended during corticosteroid therapy to reduce the risk of gastric ulceration.

There are drugs and other therapies to either prevent or manage many side effects. **For more information, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) and filter by Side-Effect Management to view, print or order the free LLS series *Side Effects Management*.**

Sometimes drugs or drug combinations cause side effects that continue after treatment ends. Some effects may be long-lasting (see *Long-Term and Late Effects of Treatment* on page 50).

## Coping with Hair Loss in Children

For many children, hair loss can be one of the most distressing side effects of cancer treatment. Children can be sensitive about how they look and how others perceive them. Unfortunately, most children treated for ALL will begin to temporarily lose their hair 2 to 3 weeks after starting chemotherapy. The following information may be useful to help children cope with hair loss.

- Many children's hospitals work with organizations that help provide wigs and other head coverings to patients in need. A hospital social worker can help children explore their options, and help families understand what is or is not covered by insurance.
- If your child is planning on wearing a wig, take a picture of your child's hair (how it is usually worn) before hair loss occurs so a wig stylist can create a wig similar to your child's natural hair. In addition, you may want to snip and keep a lock of your child's hair to help match the color and texture for a wig.
- Some children cut their hair short or shave their head before their hair falls out. This may allow children to feel some control over their hair loss and make it somewhat less upsetting. Other children may want to wait and see what happens. They may also want to dye their hair a wild color or get a crazy hairstyle. However, it is important to check with your child's doctor before using any dyes or chemical products on the hair.
- Some children like to wear wigs, hats, caps, scarves or turbans. Consider different head coverings. Shopping for head coverings can give your child some sense of control.
- Some children, particularly younger ones, may decide not to cover their heads. It is a personal choice for children and their families. However, for children going outside in the sun, it is important to protect the very sensitive skin on their head with either a head covering or sunscreen.
- Hair loss can be very difficult for children going back to school. Hospital social workers can offer support and resources for children dealing with hair loss.

## Follow-Up Care

After your child completes treatment for ALL and is in remission, your child will need to receive follow-up care. Follow-up care involves regular medical check-ups. These check-ups may include blood work as well as other tests to look for signs of a possible relapse. The doctors will also test for other physical

or emotional problems that may develop months or years after treatment. Even if your child is feeling entirely well, it is very important to keep the follow-up appointments.

Your child will undergo frequent follow-up tests during the first year after treatment, but they will be done less often during the second and third years. Testing and check-ups may be required less frequently as time goes on, but scheduled follow-up visits should continue indefinitely. If your child participated in a clinical trial, the follow-up care and frequency of visits may be slightly different but should likewise be followed accordingly.

Each patient has a different follow-up care schedule. How often your child has follow-up visits is based on your child's subtype of ALL, overall health and the treatments received. For children with ALL, the National Comprehensive Cancer Network (NCCN) recommends the following tests during the first 3 years after treatment ends. See **Table 6** below.

**Table 6. NCCN Recommendations for Follow-Up Exams and Tests**

Year	Tests	Frequency of Tests
Year 1	• Physical exam including testicular exam for males	Every 1 to 4 months
	• CBC with differential	Every 1 to 4 months
	• Liver function tests	Every 1 to 4 months until normal test results
Year 2	• Physical exam including testicular exam for males	Every 3 to 6 months
	• CBC with differential	Every 3 to 6 months
Year 3 and on	• Physical exam, including testicular exam for males	Every 6 to 12 months
	• CBC with differential	Every 6 to 12 months
Other general procedures:		
<ul style="list-style-type: none"><li>○ Bone marrow aspiration and cerebrospinal fluid testing for suspected relapse should be done as clinically indicated. If bone marrow aspiration is done, other additional tests may include: flow cytometry, cytogenetic testing, FISH, molecular testing and MRD assessment.</li><li>○ For patients with Ph+ ALL, periodic quantification testing to measure the <i>BCR-ABL1</i> gene is recommended.</li></ul>		

Adapted from National Comprehensive Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia; 2021.

Some childhood vaccines may have been delayed during treatment. Your doctor will advise you when to resume your child's vaccination schedule. Current COVID-19 vaccines are also recommended for specific ages. Speak to your child's doctor for more information.

Your child's healthcare team may also recommend a schedule for having your child's learning skills tested. If your child appears to be struggling with learning, special education methods may help. See *Returning to School* on page 53.

Your child will continue to need follow-up care even after becoming an adult. Young adult patients need to be educated about the importance of follow-up care. When they reach adulthood, remind your child that any new providers they see will need to know their detailed medical history and survivorship care plan. Work with members of the cancer treatment team to coordinate care and transfer medical records to new providers.

It is important to keep a record of your child's cancer treatments, so that during visits for follow-up care, the doctor can watch for specific late effects that may be associated with those treatments.

**Survivorship Care Plan.** "Survivorship" generally refers to the health and well-being of a person after cancer treatment. Your child's hematologist-oncologist will help create a survivorship care plan for your child to guide follow-up care. That way, as your child enters adulthood, they will have a clear, written history of their diagnosis, treatments and schedule for follow-up care.

Share the survivorship care plan with any healthcare providers your child sees. The survivorship care plan should include the following information:

- A list of all your child's healthcare providers: pediatrician, hematologist-oncologist, radiation-oncologist, etc
- Diagnosis summaries with specifics such as stage, sites of involvement, and molecular or genetic markers
- Treatment summary with specifics such as dates of treatment, names of chemotherapy or other drugs received, radiation dosage and site, responses to treatments and side effects
- Follow-up appointment schedule with the names of the medical providers and how often the appointments should occur
- Schedule for ongoing monitoring, with recommended tests and frequency
- List of possible long-term and late effects
- Health and wellness lifestyle recommendations, such as nutrition, exercise, other cancer and disease screenings, and referrals to specialists (as needed) to assist with these recommendations

**Visit [www.LLS.org/SurvivorshipWorkbook](http://www.LLS.org/SurvivorshipWorkbook) to reach the children and adolescent, young adult and adult books called *Navigating Life During and After a Blood Cancer Diagnosis*.**

The Children's Oncology Group provides a downloadable Summary of Cancer Treatment template to fill out with your child's healthcare team. Visit [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org) to download a template.

The Passport for Care Survivor Website offers free access to resources, education and tools for survivorship for childhood cancer survivors.

Visit [www.cancersurvivor.passportforcare.org](http://www.cancersurvivor.passportforcare.org) to learn more.

**Survivorship Clinics.** Childhood cancer survivors have special lifelong healthcare needs. Many hospitals and treatment centers offer survivorship clinics that specialize in long-term follow-up care for cancer survivors. Children often begin visiting a survivorship clinic 2 years after completing cancer treatment. However, the timeline can differ based on your child's unique needs and medical history. Additionally, coordination between members of your child's cancer survivorship healthcare team and primary care pediatrician is essential.

Your child should visit the survivorship clinic and primary care pediatrician at least once a year for a complete physical examination and any other necessary tests, even when your child feels well. Regular visits allow the doctor to:

- Assess the full effects of therapy
- Identify and manage long-term and late effects of treatment (see *Long-Term and Late Effects of Treatment* below)
- Detect and treat disease relapse

In preparation for your child's visits, keep a record of the physical or emotional symptoms that your child experiences so that you can discuss them with members of the healthcare team. For example, children may experience difficulties when they return to their daily routines after a long period of treatment. Getting support throughout this time, and for as long as needed, is important.

**Long-Term and Late Effects of Treatment.** Cancer treatments can harm a child's organs, tissues or bones and may cause delayed growth and other health problems later in life. Childhood cancer survivors may have complex and long-term health issues due to the treatments they receive. While treatments for ALL have led to increased survival rates, some may cause significant long-term or late effects.

"Long-term effects" of cancer treatment are medical problems that last for months or years after treatment ends. Examples of long-term effects are infertility, growth problems and treatment-related fatigue. "Late effects" are

medical problems that do not appear until years, or even possibly decades, after treatment ends. Examples of late effects include the development of a treatment-related cancer or heart disease.

For survivors of childhood leukemia, long-term and late effects of treatment may involve:

- Cognitive (learning) effects
- Physical development
- Psychological development

Factors that influence a child's risk for developing long-term or late effects include:

- Type and duration of treatment
- Sex
- Age at the time of treatment
- Overall health

The range and severity of these potential long-term and late effects vary. Some children have no significant long-term or late effects, or very mild effects, while others have serious complications. Some late effects become evident with the onset of puberty, growth, and the normal aging process. Early intervention and healthy lifestyle practices (not smoking, good nutrition and exercise, regular screenings and follow-up care) may have a positive effect on the occurrence and/or severity of effects.

It is important for parents to discuss possible late effects with members of their child's healthcare team so that the proper planning, evaluation and follow-up care can take place.

**Types of Long-Term and Late Effects.** Long-term and late effects of ALL treatment may include cognitive, physical and psychological effects.

**Cognitive (Learning) Effects.** Treatments directed at the central nervous system, such as intrathecal chemotherapy, radiation to the brain, and intravenous chemotherapy with high-dose **methotrexate** or **cytarabine**, are effective therapies used to treat children with ALL. However, these treatments can increase the risk for cognitive effects, such as long-term memory and concentration problems. Cognitive late effects can affect your child's ability to learn and think.

Learning difficulties can range from mild to severe and can begin either during treatment or may become evident months or even years after treatment.

Mathematics, spatial relationships, problem solving, attention span, reading and spelling, processing of information, planning and organizing, and concentration skills are all areas of learning that may be affected. Problems with fine motor coordination, which might cause poor handwriting, can also develop.

Talk to your child's healthcare team about any educational or learning issues that cause concern. A pediatric psychologist can perform neuropsychological testing to evaluate your child for any signs of these potential late effects.

**See the free LLS book *Learning & Living with Cancer: Advocating for Your Child's Educational Needs* for information about planning for your child's entry or return to school following diagnosis and treatment.**

**Second Cancer Risk.** Survivors of childhood ALL are at an increased risk for developing a second cancer later in life. A second cancer may occur months or years after treatment is completed. Because of this risk, it is important for patients who have been treated for ALL to get routine cancer screenings.

These cancer screenings should be a shared responsibility between your child's primary care doctor and oncologist. In addition, lifestyle modifications that reduce the risk for a second cancer should be encouraged, such as exercising, maintaining a healthy weight, and not smoking.

**Cardiovascular System.** Most ALL patients are treated with an anthracycline, such as **doxorubicin** or **daunorubicin**. Anthracyclines have been associated with increased risk for heart muscle injury or chronic heart failure. Heart disease may not become apparent until many years after treatment ends. Talk to your child's doctor about whether tests are needed to check for signs of heart and blood vessel-related late effects. If tests are recommended, find out how often they should be done.

**Osteonecrosis.** Osteonecrosis, also called "avascular necrosis," is a condition in which there is a reduced blood flow to the bones. This can cause parts of the bones to weaken or die, which can cause pain or even breaks in the bone. Osteonecrosis often affects weight-bearing joints, such as the hip bones and/or knees. Osteonecrosis is a long-term side effect associated with corticosteroid therapy. This condition seems to have a higher incidence among adolescents than in younger children or adults (likely due to skeletal growth). Your medical team may recommend checking vitamin D and calcium levels if your child is at risk for this condition. If your child is having pain, imaging studies may be indicated or may be performed as part of a clinical trial.

**Psychological Effects.** Most childhood survivors of cancer are psychologically healthy. However, some studies indicate that a small number of childhood leukemia survivors were more likely than healthy peers to report changes in behavior, feelings or mood, including depression or post-traumatic stress disorder (PTSD). Talk to your child's healthcare team if you notice any changes in your child's mood or behavior, especially if these changes begin to interfere with your child's daily life.

**Visit [www.LLS.org/FamilyWorkbook](http://www.LLS.org/FamilyWorkbook) to find additional information about long-term and late effects (in the chapter *Beyond Treatment*).**

### Talk to your doctor about

- Possible long-term and late effects and follow-up care

**Returning to School.** School is a place for learning and fun, so children benefit from returning to their classrooms as soon as medically possible. Most children who have cancer will attend school at least some of the time during their treatment. Yet returning to school after a diagnosis of cancer can be a difficult adjustment. Your child may have reservations about returning to school, including fears about:

- The reaction of friends and other children at school
- Missed schoolwork and social activities
- Changes in their abilities
- Changes in their appearance

Discuss with your child any fears they may have before going back to school. Help your child develop coping strategies for situations that may happen.

If your child has been out of the classroom for an extended time, it may be helpful to ease back into full-time school slowly. For example, your child may attend school for half days or every other day during the first weeks back. Talk to school administrators about adjustments to schedules and other options available.

Take the following steps to ensure that your child gets the support needed at school:

- Meet with school administrators, teachers, counselors and the school nurse as soon as you can after diagnosis to discuss your child's medical condition and address any special needs or concerns.
- Discuss any evaluations that may be needed to provide your child with extra support, such as neuropsychological testing. Ask school staff members to provide you with relevant information promptly when they identify any issues that arise.
- Work with the school nurse to make sure that a care plan is in place that addresses your child's medical needs during school hours. For example,
  - Your child may need to take medications at school. These may be daily medications or medications taken as needed (for example, when your child feels nauseated).
  - If your child has a catheter or some other medical device in place, make sure the school nurse knows how to care for the device properly.
  - The care plan should also include a list of issues that can come up, reasons to contact you and when to call for emergency care. Your child's healthcare team can help the school nurse develop a care plan and fill out any necessary paperwork.

- Ask your child's doctor to write a letter outlining your child's physical limitations or medical needs, such as the need for an extra snack or cool drinks, extra bathroom breaks and/or a safe place to rest, as needed. Modifications may also be needed for recess or physical education (P.E.) classes. Meet with school administrators and teachers to discuss these needs and how they will be accommodated. Ask your child's healthcare team for their expertise in explaining this information.
- To reduce your child's anxiety, arrange meetings with the teacher(s) before your child goes back to school.
- Ask about providing an age-appropriate class presentation, either before or after your child returns to school, to educate friends and classmates about cancer. Ask the healthcare team for assistance. Some treatment centers have healthcare professionals available to lead these presentations, or they may have already-prepared versions of these presentations available for use. Ask your child if they would like to be in the class for the presentation. If so, your child can participate in ways that they feel comfortable.

For more information about returning to school after cancer treatment, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to view ***Learning and Living with Cancer***.

***The Trish Greene Back to School Program.*** This LLS program offers free information and materials to parents and educators that can help ease a child back into school. The program was developed to encourage communication among parents, patients, healthcare professionals and school personnel to assure that children have a smooth transition from undergoing active treatment to settling back into school. Call an LLS Information Specialist at **(800) 955-4572** to learn more.

## Treatment Outcomes

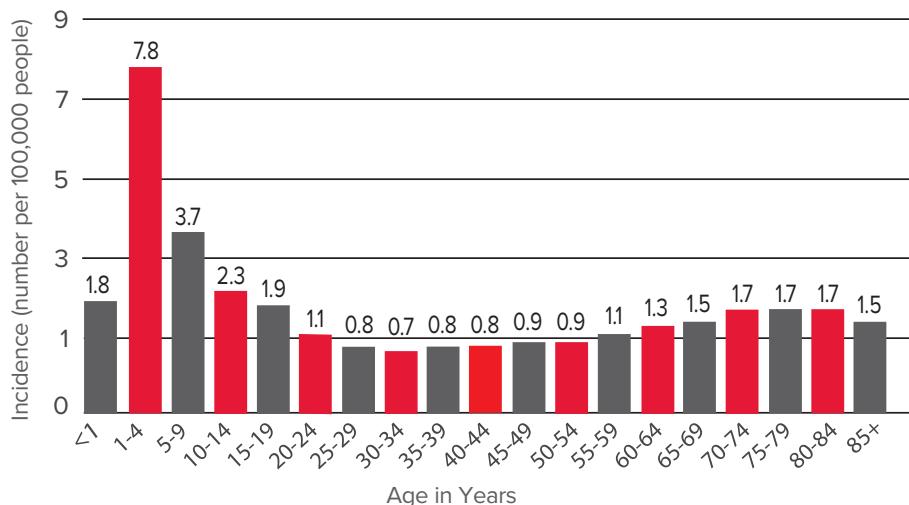
A few decades ago, there were very low cure rates in both children and adults diagnosed with ALL. Today, childhood ALL has one of the highest cure rates of all childhood cancers, approaching 92 percent for children younger than 15 years, and more than 94 percent for children younger than 5 years.

## Incidence, Causes and Risk Factors

**Incidence.** ALL is rare in children. An average of 2,826 children and young adults younger than 20 years of age were diagnosed with leukemia each year from 2014 to 2018 in the United States.

There is an unusual age distribution among people with ALL. The incidence of ALL peaks between the ages of 1 and 4 years and then decreases until about age 55 years. See **Figure 6** below.

**Figure 6. Age-Specific Incidence Rates for Acute Lymphocytic Leukemia (All Races): 2014-2018**



Source: SEER\*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2021 September 27]. Available from <https://seer.cancer.gov/explorer/>.

**Causes and Risk Factors.** In most cases, it is not clear what causes the genetic changes that lead to ALL, particularly in children. Researchers are trying to understand why these changes occur and how they cause ALL to develop. Not all patients with ALL have the same genetic mutations, and some genetic changes are more common than others.

Although the cause is unknown, there are some known risk factors for ALL. A “risk factor” is anything that increases a person’s chance of developing a disease. However, having a risk factor does not mean that a person will develop the disease. Some people with several risk factors for a disease may never develop it, while others with no known risk factors may develop the disease. ALL is not contagious.

Factors associated with an increased risk of developing ALL include:

- Genetic disorders. Certain genetic conditions present at birth seem to increase the risk of ALL including Down syndrome, neurofibromatosis, Klinefelter syndrome, Fanconi anemia, Shwachman-Diamond syndrome, Bloom syndrome, Li-Fraumeni syndrome and ataxia-telangiectasia.
- Age. The highest incidence rates for ALL are seen in children and adolescents younger than 15 years. Within this group, the highest rate is in children aged 1 to 4 years.

- Sex. Males are more likely to develop ALL than females.
- Race/ethnicity. In the United States, ALL is more common in Hispanics and whites.
- Exposure to chemotherapy and radiation therapy. People who have received certain types of chemotherapy and radiation therapy may have an increased risk of developing ALL. However, this is not common in children.

## Drugs Used in the Treatment of ALL

For more information, please see the Package Insert and/or the Full Prescribing Information for each medication on the internet.

Drug Name	Administration	FDA-Approved Indications
<b>Alkylating Agents (DNA-Damaging Drugs):</b> These drugs work by stopping or slowing the growth of cancer cells by damaging the DNA.		
Cyclophosphamide (Cytoxan®)	Intravenous (IV) Oral	Approved for the treatment of leukemia
<b>Anthracyclines:</b> These drugs damage the DNA in cancer cells, causing them to die.		
Daunorubicin (Cerubidine®)	Intravenous (IV)	Approved for the treatment in combination with other approved anticancer drugs for remission induction in acute lymphocytic leukemia of children and adults
Doxorubicin (Adriamycin®)	Intravenous (IV)	Approved for the treatment of acute lymphoblastic leukemia
Mitoxantrone (Novantrone®)	Intravenous (IV)	Approved for the treatment of acute nonlymphocytic leukemia and is being studied in clinical trials for the treatment of ALL
<b>Antimetabolites:</b> These drugs interfere with the normal division and functions of cancer cells.		
Clofarabine (Clolar®)	Intravenous (IV)	Approved for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute ALL after at least two prior regimens
Cytarabine (cytosine arabinoside, ARA-C; Cytosar-U®)	Intravenous (IV) Subcutaneously (under the skin) Intrathecal	Approved to be used alone or with other chemotherapy drugs to treat certain types of leukemia including ALL. Intrathecal administration of cytarabine injection (preservative-free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.
Fludarabine (Fludara®)	Intravenous (IV)	Approved for the treatment of chronic lymphocytic leukemia (CLL) and is being studied in clinical trials for the treatment of ALL
Mercaptopurine (6-MP, Purinethol®, Purixan®)	Oral	Approved for the treatment of patients with ALL as part of a combination regimen

Methotrexate (Xatmep®, Abitrexate®, Trexall®)	Intravenous (IV) Intramuscular Oral	Approved for the treatment of adult and pediatric patients with ALL as part of combination chemotherapy regimen. Prophylaxis and treatment of adult and pediatric patients with meningeal leukemia
Nelarabine (Arranon®)	Intravenous (IV)	Approved for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in adult and pediatric patients age 1 year and older whose disease has not responded or has relapsed following treatment with at least two chemotherapy regimens
6-thioguanine (thioguanine, Tabloid®)	Oral	Approved for the treatment of acute myeloid leukemia (AML) but may be used as an off-label treatment for ALL.
<b>Enzyme Therapy:</b> A type of treatment that uses an enzyme taken from the bacterium Escherichia coli (E. coli). It breaks down the amino acid asparagine and may block the growth of cancer cells that need asparagine to grow.		
Asparaginase Erwinia chrysanthemi (Rylaze™, Erwinaze®)	Intramuscular injection	Approved as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase
Calaspargase pegol-mknl (Asparlas™)	Intravenous (IV)	Approved as a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia in pediatric and young adult patients age 1 month to 21 years
Pegaspargase (PEG-L asparaginase, Oncaspar®)	Intramuscular injection Intravenous (IV)	Approved as a component of multi-agent chemotherapeutic regimen for treatment of pediatric and adult patients with: <ul style="list-style-type: none"><li>• First-line acute lymphoblastic leukemia</li><li>• Acute lymphoblastic leukemia and hypersensitivity to asparaginase</li></ul>
<b>Plant Alkaloids:</b> Chemotherapy treatments made from certain types of plants. They are cell-cycle specific, meaning they attack the cancer cells during various phases of division.		
Vincristine (Oncovin®)	Intravenous (IV)	Approved for the treatment of acute leukemia
<b>Topoisomerase Inhibitor:</b> A type of drug that blocks topoisomerases (enzymes that break and rejoin DNA strands and are needed for cells to divide and grow). Blocking these enzymes may kill cancer cells.		
Etoposide (VP-16, VePesid®, Etopophos®)	Intravenous (IV) Oral	Used as an off-label treatment for ALL

<b>Corticosteroids:</b> This type of drug is made in the laboratory and is similar to a natural hormone that is made by the adrenal glands. Corticosteroids help destroy leukemia cells.		
Dexamethasone	Oral	Approved for the treatment of ALL
Hydrocortisone	Oral	Approved for the treatment of ALL
Prednisone	Oral	Approved for the treatment of ALL
<b>Tyrosine Kinase Inhibitors:</b> This type of drug blocks the enzyme tyrosine kinase, which causes stem cells to develop into more white blood cells than needed.		
Imatinib (Gleevec®)	Oral	Approved for the treatment of pediatric patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy
Dasatinib (Sprycel®)	Oral	Approved for the treatment of pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy
Ruxolitinib (Jakafi®)	Oral	A JAK1/JAK2 inhibitor being tested in clinical trials for the treatment of Ph-like ALL
<b>Immunotherapies:</b> These types of drugs use substances to stimulate or suppress the immune system to help the body fight cancer.		
Blinatumomab (Blincyto®)	Intravenous (IV)	Approved for the treatment of adults and children with: <ul style="list-style-type: none"> <li>• CD 19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%</li> <li>• Relapsed or refractory CD 19-positive B-cell precursor acute lymphoblastic leukemia (ALL)</li> </ul>
Tisagenlecleucel (Kymriah®)	Intravenous (IV)	A CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
Daratumumab (Darzalex®)	Intravenous (IV)	A monoclonal antibody directed against CD38 that is being studied in children with relapsed T-cell ALL
Inotuzumab ozogamicin (Besponsa®)	Intravenous (IV)	This treatment is not currently approved to treat ALL but is being studied in clinical trials

# Normal Blood and Bone Marrow

**Blood.** Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

**Plasma.** Plasma is largely made up of water, in which many chemicals are dissolved. These chemicals each have a special role. They include:

- Proteins
  - Albumin, the most common blood protein
  - Blood-clotting proteins (coagulation factors) made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
  - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B<sub>12</sub>
- Electrolytes, such as calcium, potassium and sodium

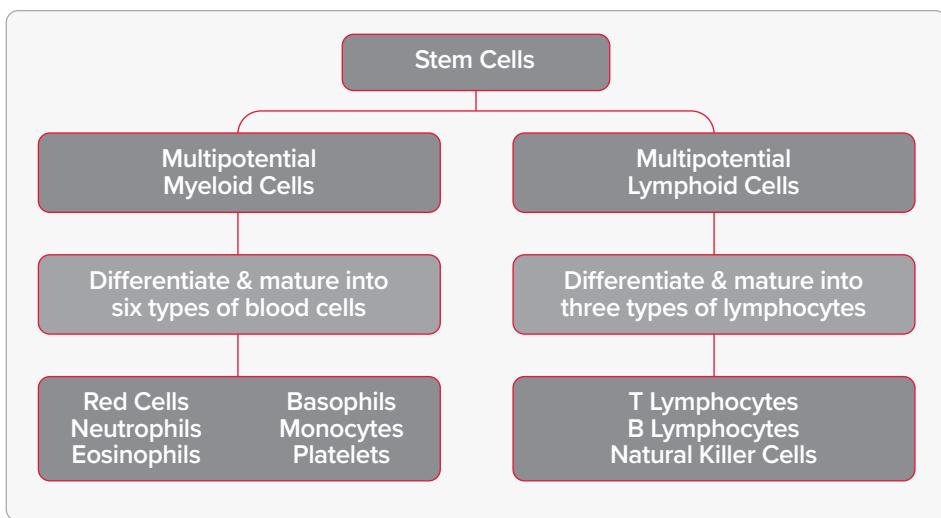
**Blood cells.** Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." See **Figure 7** on page 60. The blood cells are suspended in the plasma.

Once the stem cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
  - These make up a little less than half of the body's total blood volume.
  - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO<sub>2</sub>) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO<sub>2</sub> is removed from the lungs.
2. Platelets (cells that help blood clot)
  - These are small cells (one-tenth the size of red blood cells).
  - They help stop bleeding from an injury or cut.
  - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot with the help of proteins such as fibrin, and electrolytes such as calcium.
3. White blood cells (or WBCs, the cells that fight infections), including:

- Neutrophils and monocytes. These are cells called “phagocytes” that ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
- Eosinophils and basophils. These are the WBCs that respond to allergens or parasites.
- Lymphocytes. These are the WBCs found mostly in the lymph nodes, spleen and lymphatic channels that are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
  - T lymphocytes (T cells)
  - B lymphocytes (B cells)
  - Natural killer cells (NK cells)

**Figure 7. Blood Cell & Lymphocyte Development**



Stem cells develop into blood cells (hematopoiesis) and lymphocytic cells.

**Bone Marrow.** In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as it passes through the marrow and then circulates throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream

and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

## The Lymphatic System

The marrow is really two organs in one. It is (1) the organ that forms blood cells, and it is (2) the organ that forms lymphocytes, which make up part of the immune system.

The marrow produces three main types of lymphocytes. They are

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and ingests the microbe.
- Natural killer (NK) cells, which have granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system, such as the skin, spleen, tonsils and adenoids, intestinal lining, and (in young people) the thymus.

# Resources and Information

LLS offers free information and services for patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

## For Help and Information

**Consult with an Information Specialist.** Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date information about disease, treatment and support. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)

**Clinical Trials (Research Studies).** Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Patients and caregivers can work with Clinical Trial Nurse Navigators who will help find clinical trials and personally assist them throughout the entire clinical trial process. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**One-on-One Nutrition Consultations.** Access free one-on-one nutrition consultations provided by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management, and survivorship nutrition. They also provide additional nutrition resources. Please visit [www.LLS.org/nutrition](http://www.LLS.org/nutrition) for more information.

**Free Information Booklets.** LLS offers free education and support booklets that can either be read online or ordered. Please visit [www.LLS.org/booklets](http://www.LLS.org/booklets) for more information.

**Telephone/Web Education Programs.** LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit [www.LLS.org/programs](http://www.LLS.org/programs) for more information.

**Financial Assistance.** LLS offers financial support, including insurance premium and medication co-pay assistance, to eligible individuals with blood cancer. For more information, please:

- Call: (877) 557-2672
- Visit: [www.LLS.org/finances](http://www.LLS.org/finances)

**LLS Health Manager™ App.** This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and

share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Please visit [www.LLS.org/HealthManager](http://www.LLS.org/HealthManager) to download for free.

**LLS Coloring for Kids™.** This free coloring app allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages and pages from LLS coloring books. This app can be used anywhere and may help pass time in waiting rooms or during treatment. Visit [www.LLS.org/ColoringApp](http://www.LLS.org/ColoringApp) to learn more and download.

**Podcast.** *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit [www.LLS.org/TheBloodline](http://www.LLS.org/TheBloodline) for more information and to subscribe.

**Suggested Reading.** LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit [www.LLS.org/SuggestedReading](http://www.LLS.org/SuggestedReading) to find out more.

## Community Resources and Networking

**LLS Community.** The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit [www.LLS.org/community](http://www.LLS.org/community) to join.

**Weekly Online Chats.** Moderated online chats can provide support and help cancer patients reach out and share information. Please visit [www.LLS.org/chat](http://www.LLS.org/chat) for more information.

**LLS Chapters.** LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact your chapter, please:

- Call: (800) 955-4572
- Visit: [www.LLS.org/ChapterFind](http://www.LLS.org/ChapterFind)

**Other Helpful Organizations.** LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit [www.LLS.org/ResourceDirectory](http://www.LLS.org/ResourceDirectory) to obtain the directory.

**Advocacy.** The LLS Office of Public Policy (OPP) enlists volunteers to advocate for policies and laws to speed new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: [www.LLS.org/advocacy](http://www.LLS.org/advocacy)

## **Additional Help for Specific Populations**

**Información en Español (LLS information in Spanish).** Please visit [www.LLS.org/espanol](http://www.LLS.org/espanol) for more information.

**Language Services.** Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

**Information for Veterans.** Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the VA (800) 749-8387
- Visit: [www.publichealth.va.gov/exposures/AgentOrange](http://www.publichealth.va.gov/exposures/AgentOrange)

**World Trade Center Survivors.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: [www.cdc.gov/wtc/faq.html](http://www.cdc.gov/wtc/faq.html)

**People Suffering from Depression.** Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a two-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at [www.nimh.nih.gov](http://www.nimh.nih.gov) and enter “depression” in the search box

# Health Terms

**Adrenal Gland.** A small gland near the kidneys that makes steroid hormones. These hormones help control heart rate, blood pressure and other important body functions. They also help reduce inflammation.

**Alkylating Agent.** A type of chemotherapy drug used in cancer treatment. It kills cancer cells by damaging their DNA, which prevents them from dividing (reproducing).

**Allogeneic Stem Cell Transplantation.** A treatment that uses healthy donor stem cells to restore a patient's damaged or diseased bone marrow after receiving high doses of chemotherapy and/or radiation therapy. **See the free LLS book *Blood and Marrow Stem Cell Transplantation*.**

**Anemia.** A condition in which the number of red blood cells is below normal. This results in reduced oxygen flow to the body's organs. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath.

**Anthracycline.** A type of chemotherapy used to treat many types of cancer. Anthracyclines damage the DNA of cancer cells, causing them to die.

**Antibody.** A type of protein created by blood cells in response to an antigen (a substance that causes the body to mount a specific immune response). Antibodies help the body fight against invaders that make a person sick. Antibodies can also be made in the laboratory and are used to help identify certain types of cancer and to help treat cancer.

**Antigen.** A substance that creates an immune response in the human body, especially the production of antibodies. Examples include allergens, chemicals, bacteria, viruses and other substances outside the body. Cells in the body, including cancer cells, also have antigens on them that can cause an immune response. Antigens can also be used as markers in laboratory tests to identify certain cancer cells.

**Basophil.** A type of white blood cell that participates in certain allergic reactions.

**B Cell.** A type of white blood cell called a lymphocyte. B cells are part of the immune system. They produce antibodies that attack bacteria, viruses and toxins.

**Biopsy.** A procedure to remove a sample of cells or tissue from the body for examination by a pathologist. The pathologist may study the specimen under a microscope or perform other tests on the cells or tissue.

**Blast Cell.** An immature blood cell.

**Blood Cell Count.** See Complete Blood Count.

**Blood Cells.** There are three main types of blood cells: 1) red blood cells that carry oxygen; 2) white blood cells that fight infections; and 3) platelets that help stop bleeding.

**Bone Marrow.** The spongy tissue in the center of most bones, where blood cells form.

**Bone Marrow Aspiration.** A procedure in which a sample of liquid bone marrow is removed for examination by a pathologist. After the patient is given a numbing agent, the sample is taken (usually from the patient's hip bone) using a special needle. Bone marrow aspiration and bone marrow biopsy are often done at the same visit, and may be done in the doctor's office or in a hospital. When this procedure is done in children, they are usually under sedation or general anesthesia.

**Bone Marrow Biopsy.** A procedure in which a sample of bone with bone marrow is removed for examination by a pathologist. The sample is usually taken from the hip bone. After medication is given to numb the skin and tissue, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy are often done at the same visit, and may be done in the doctor's office or in a hospital. When this procedure is done in children, they are usually under sedation or general anesthesia.

**CBC.** See Complete Blood Count.

**Central Line (Central Venous Catheter).** A flexible tube used to deliver medications, fluids or blood products into the body or to withdraw blood samples from the body. See Port.

**Central Nervous System (CNS) Prophylaxis.** Treatment given to lower the risk of leukemia cells spreading to the central nervous system (brain and spinal cord). The treatment may include intrathecal chemotherapy (chemotherapy directly injected into the cerebrospinal fluid, the space between the layers of tissue that cover the brain and spinal cord), high-dose chemotherapy injected into a vein, or radiation therapy.

**Cerebrospinal Fluid.** A clear, colorless liquid that surrounds the brain and spinal cord.

**Chemotherapy.** Treatment that stops the growth of cancer cells, either by killing the cancer cells or by stopping them from dividing.

**Chimeric Antigen Receptor (CAR) T-Cell Therapy.** Treatment that uses a patient's own T cells (a type of white blood cells) to identify and attack cancer cells. The T cells are taken from the patient's blood and sent to a

laboratory where they are genetically modified to attack cancer cells. The engineered T cells are then multiplied and eventually re-infused into the patient's blood stream. **See the free LLS fact sheet *Chimeric Antigen Receptor (CAR) T-Cell Therapy*.**

**Chromosome.** Part of the cell that contains genes in a linear order. Human cells have 23 pairs of chromosomes, or a total of 46 chromosomes. **See the free LLS book *Understanding Genetics*.**

**Clinical Trial.** A carefully planned and monitored research study to evaluate how well new medical approaches work in patients. The goal of clinical trials for blood cancers is to develop new treatments, improve quality of life and increase survival.

**Complete Blood Count (CBC).** A laboratory test that measures the number of red blood cells, white blood cells, and platelets in the blood. It also measures the amount of hemoglobin (the substance in the blood that carries oxygen) and the hematocrit (the amount of whole blood that is made up of red blood cells).

**Computed Tomography (CT) Scan.** A procedure in which a computer linked to an x-ray machine is used to take a series of detailed pictures of areas inside the body. In some cases, leukemia may grow outside the bone marrow—most commonly in the lymph nodes. A CT scan may be used to see whether leukemia cells are accumulating in lymph nodes in the chest or abdomen, or in organs such as the spleen and liver.

**Conditioning Therapy.** Intensive treatment used to prepare a patient for stem cell transplantation. The treatment consists of high-dose chemotherapy and/or total body radiation.

**Conscious Sedation.** A combination of medicines to help a patient relax and to block pain during a medical procedure. A person is asleep but wakes when spoken to or touched.

**Cytogenetic Analysis.** The process of analyzing the number and size of the chromosomes in cells. It detects chromosome alterations and, in some cases, may identify the actual genes that have been affected. These findings help doctors diagnose specific types of blood cancer, determine appropriate treatment approaches, and monitor a treatment response in patients.

**DNA.** Abbreviation for deoxyribonucleic acid, which is the material found inside cells that carries genetic information. A change or mutation in the DNA can lead to cell death, changes in the cell function and, in some cases, cancer.

**Echocardiogram.** A computer-generated picture of the heart created by bouncing sound waves (ultrasound) off internal tissues or organs of the chest. An echocardiogram shows the size, shape and position of the heart. It also shows parts inside the heart. An echocardiogram may be used to help diagnose heart problems.

**Eosinophil.** A type of white blood cell that travels to affected areas during infections and allergic reactions.

**Erythrocyte.** Another word for red blood cell. See Red Blood Cell.

**Extramedullary Disease.** Leukemia cells found outside of the bone marrow and blood.

**FDA.** The abbreviation commonly used to refer to the United States Food and Drug Administration. The FDA is responsible for assuring the safety, effectiveness and security of drugs, medical devices and the nation's food supply.

**First-Line Therapy.** The first treatment given for a disease.

**FISH.** A test that can help diagnose cancer. See Fluorescence in Situ Hybridization (FISH).

**Flow Cytometry.** A test that measures certain characteristics of cells in a sample, including the size, shape and presence of tumor markers on the cell's surface. During this test, cells flow through an instrument called a "flow cytometer." When the cells pass through its laser beam, those with antibody-specific features light up and can be counted.

**Fluorescence in Situ Hybridization (FISH).** A technique for studying abnormal chromosomes in cells and tissues. Pieces of DNA that contain fluorescent molecules are added to cells or tissues on a slide. When the pieces of DNA bind to specific genes or chromosomes, they light up when viewed under a specialized microscope. This test can help diagnose some cancers, plan treatment and monitor the effectiveness of treatment.

**General Anesthesia.** A combination of medication that puts a person in a sleep-like state before a surgery or other medical procedure. Under general anesthesia, a person does not feel pain because they are unconscious.

**Granulocyte.** A type of white blood cell with many particles (granules). Neutrophils, eosinophils and basophils are types of granulocytes.

**Hematologist.** A doctor who specializes in treating blood cell diseases.

**Hematopathologist.** A doctor who has special training in identifying diseases of the blood cells by examining blood, bone marrow, lymph tissue and other body fluids under a microscope.

**Hematopoiesis.** The formation of new blood cells. For information on the blood cell development process, see *Normal Blood and Bone Marrow* on page 59.

**Hematopoietic Stem Cell.** An immature cell that can develop into any type of blood cell: a red blood cell, a white blood cell or a platelet. Also called a “blood stem cell.”

**Hemoglobin.** The iron-containing substance in red blood cells that carries oxygen around the body. Hemoglobin concentration decreases when there is a reduction in the number of red blood cells. This condition is called “anemia.”

**Human Leukocyte Antigen (HLA).** A type of protein found on cells that helps the body distinguish its own cells from foreign cells. HLA factors are inherited from a person’s mother and father. HLAs make up an individual’s tissue type, which varies from person to person. They are a critically important factor in allogeneic (donor) stem cell transplantation. Before transplantation takes place, HLA typing is performed to determine if the donor’s cells are compatible with the recipient’s cells.

**Hyperdiploidy.** In humans, cells that have more than the normal 46 chromosomes.

**Hypodiploidy.** In humans, cells that have less than the normal 46 chromosomes.

**Immune System.** A complex network of cells, tissues and organs that work together to defend the body against infections.

**Immunophenotyping.** A process that uses antibodies to find specific types of cells based on the types of antigens (markers) on the surface of the cells.

**Immunotherapy.** The term for several treatment approaches used by doctors to harness the body’s immune system to treat leukemia and other diseases. These therapies include antibody therapies (monoclonal, bispecific and antibody-drug conjugates), radioimmunotherapy and cellular therapy.

**Intrathecal Chemotherapy.** Treatment in which anticancer drugs are injected into the cerebrospinal fluid to kill any leukemia cells that may have spread to the brain or spinal cord.

**Karyotype.** An organized profile of a person's chromosomes. It exhibits the size, shape and number of chromosomes in a cell.

**Late Effect.** A medical problem that either does not appear or is not noticed until years after treatment ends. Treatment-related cancer and heart disease are examples of late effects.

**Leukocyte.** Another word for white blood cell. See White Blood Cell.

**Lumbar Puncture.** A procedure in which a thin needle is inserted into the spinal column to collect cerebrospinal fluid or to administer anticancer drugs to the central nervous system (CNS). Another term for lumbar puncture is "spinal tap."

**Lymph Node.** A bean-shaped structure that is part of the body's immune system. Throughout the body, there are hundreds of lymph nodes that contain large numbers of lymphocytes, which are white blood cells that help fight infection and disease. See Lymphocyte.

**Lymphocyte.** A type of white blood cell that is important to the body's immune system. There are three major types of lymphocytes: 1) B lymphocytes (B cells), which produce antibodies to help combat infections; 2) T lymphocytes (T cells), which have several functions, including assisting B lymphocytes (B cells) in making antibodies; and 3) natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

**Lymphoid.** Referring to lymphocytes (a type of white blood cell).

**Macrophage.** A type of white blood cell that surrounds and kills micro-organisms, eats dead cells, and helps lymphocytes with their immunity functions.

**Marrow.** See Bone Marrow.

**Minimal Residual Disease (MRD).** The small amount of cancer cells that may remain in the body after treatment. These residual cells can only be found by very sensitive tests. **See the free LLS fact sheet *Minimal Residual Disease*.**

**Monoclonal Antibody.** A type of protein made in a laboratory that can bind to certain targets in the body, such as antigens on cancer cells. Monoclonal antibodies are used to treat some types of cancer.

**Monoclonal Antibody Therapy.** Targeted treatment using proteins made in the laboratory that either react with or attach to targeted antigens on certain cancer cells. Monoclonal antibodies can be used alone or to carry drugs, toxins, or radioactive substances directly to cancer cells.

**Monocyte/Macrophage.** A type of white blood cell made in the bone marrow. Some monocytes travel through the blood to tissues in the body, where they become macrophages. Macrophages can combat infection in the tissues, ingest dead cells and assist lymphocytes in their immune functions.

**Mutation.** A change in the DNA sequence of a cell. A mutation may be caused by an error in cell division or by contact with DNA-damaging substances in the environment.

**Neutropenia.** A condition in which the number of neutrophils, a type of white blood cell, is below normal. People with neutropenia are susceptible to infections.

**Neutrophil.** A type of white blood cell, and the principal type of phagocyte (microbe-eating cell), in the blood. It is the main type of cell that combats infection. People with blood cancer, or who have received treatment (such as chemotherapy) for cancer, often have low neutrophil counts.

**Off-Label.** Describes the legal use of a prescription drug to treat a disease for which the drug has not been approved by the FDA.

**Oncologist.** A doctor who has special training in diagnosing and treating cancer.

**Oral Therapy.** Treatment that is taken by mouth.

**Pathologist.** A doctor who has special training in identifying diseases by studying cells and tissues under a microscope.

**Petechiae.** Pinhead-sized red or purple spots under the skin, caused by bleeding. It may occur due to a low platelet count.

**Phagocyte.** A type of white blood cell that protects the body from infection by eating and killing microorganisms such as bacteria and fungi. Neutrophils and monocytes are the two main types of phagocytes. When an infection occurs, phagocytes migrate from the bloodstream and enter the infected tissue.

**Philadelphia Chromosome (Ph Chromosome).** An abnormality of chromosome 22 that occurs when parts of chromosome 9 and chromosome 22 break off and trade places. The result is a chromosome 22 that is shorter than normal. The exchange of DNA between chromosomes 9 and 22 results in the creation of a fusion gene, called *BCR-ABL1*, on chromosome 22.

**Plasma.** The liquid portion of the blood, in which the blood cells, platelets, proteins and various other components are suspended. Also referred to as “blood plasma.”

**Platelet.** A small, colorless blood cell fragment that helps control bleeding. Platelets travel to and then collect at the site of a wound. The platelets' sticky surfaces help them to form clots at the site of the wound and stop bleeding. Also called "thrombocyte."

**Polymerase Chain Reaction (PCR).** A very sensitive genetic laboratory technique used to detect and measure genetic mutations and chromosomal changes that are too small to be seen with a microscope. PCR testing essentially increases (amplifies) small amounts of specific pieces of DNA so they are easier to detect and measure. This test can detect the presence of one blood cancer cell among 100,000 healthy blood cells.

**Port.** A small device that is used to withdraw blood and administer treatments such as intravenous fluids, drugs and blood transfusions. The port is placed under the skin, usually in the chest. It is attached to a catheter, a thin, flexible tube that is threaded into a large vein.

**Positron Emission Tomography (PET) Scan.** An imaging test in which a small amount of radioactive glucose (sugar) is injected into a patient's vein. The PET scanner detects areas in the body where large amounts of glucose are being used. In the images, the cancer cells appear brighter than the normal cells because they use glucose more quickly than normal cells. A PET scan may be done to see if there are cancer cells in the lymph nodes or organs.

**Prognosis.** The probable outcome or expected course of a disease; the likelihood of recovery or recurrence of disease.

**Protocol.** A plan for medical treatment.

**Radiation Therapy.** The use of x-rays and other forms of radiation to kill cancer cells.

**Recurrence.** The return of a disease after it has been in remission following treatment.

**Red Blood Cell.** A type of blood cell that contains a protein called hemoglobin. Hemoglobin carries oxygen from the lungs to the tissues of the body. Red blood cells make up about 40 to 45 percent of blood volume in healthy people. Also called "erythrocyte."

**Refractory Cancer.** Cancer that does not go into remission or improve substantially after treatment.

**Regimen.** A treatment plan that specifies the dosage, the schedule and the duration of treatment.

**Relapse.** A return of disease after a period of improvement.

**Remission.** When signs of a disease disappear, usually following treatment.

**Resistant to Treatment.** When cancer cells continue to grow, even after administration of intensive treatment, the cancer is “resistant” to that treatment. This may occur at the beginning of treatment, or may happen with a treatment after some time.

**Risk Factor.** A scientifically established factor that increases a person’s chance of getting a disease. Risk factors can be classified as either genetic (inherited), lifestyle-related or environmental.

**RNA.** Abbreviation for ribonucleic acid, a molecule in cells that carries out the instructions in DNA (deoxyribonucleic acid) for making proteins.

**Spinal Tap.** See Lumbar Puncture.

**Spleen.** An organ that is located above the stomach and under the ribs on the left side. The spleen makes lymphocytes, filters blood, stores blood cells and destroys old blood cells.

**Stem Cell.** A cell from which other types of cells develop. In the bone marrow, blood-forming stem cells mature into three major types of blood cells: red blood cells, white blood cells, and platelets. Stem cells can be collected, preserved, and used for stem cell therapy.

**Stem Cell Transplantation.** See Allogeneic Stem Cell Transplantation.

**T cell.** A type of white blood cell and specifically, a type of lymphocyte. T cells are part of the immune system that help protect the body from infection and may help fight cancer.

**Thrombocytopenia.** A condition in which the number of platelets in the blood is below normal.

**Toxin.** A naturally derived substance that is poisonous to cells. A toxin can be attached to antibodies that then attach to and kill cancer cells.

**Transfusion.** A procedure in which whole blood or parts of blood are placed into a patient’s bloodstream.

**Translocation.** A chromosomal abnormality in which a piece of one chromosome breaks off and attaches to another chromosome. The location at which the break occurs may affect nearby genes and lead to medical problems. See Mutation.

**Treatment Cycle.** A course of treatment followed by a period of rest (to allow the body to recover) that is repeated on a regular schedule. For example, chemotherapy given daily for 1 week followed by 2 weeks of rest, may be one patient's cycle of treatment.

**Trisomy.** The presence of three copies of a specific chromosome, instead of the normal two, in some or all of the body's cells. Down syndrome is a condition caused by trisomy. People with Down syndrome typically have three copies of chromosome 21 in each cell (normally there are two copies of chromosome 21).

**Tyrosine Kinase Inhibitor (TKI).** A type of drug that blocks the action of enzymes called "tyrosine kinases." Tyrosine kinases play a key role in cell function, including cell growth and division. These enzymes may be too active, or found at high levels, in some types of cancers. TKIs work to block these overactive enzymes and may stop cancer cells from growing.

**White Blood Cell.** A blood cell that is part of the body's immune system. The five major types of white blood cells are: neutrophils, eosinophils, basophils, monocytes, and lymphocytes. Also called "leukocyte."

**World Health Organization (WHO).** An agency of the United Nations that deals with major health issues around the world. The WHO sets standards for healthcare and medicines and publishes scientific papers and reports.

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## NOTES

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# Get support. Reach out to our **INFORMATION SPECIALISTS**

The Leukemia & Lymphoma Society team consists of highly trained oncology social workers, nurses and health educators who are available by phone Monday through Friday, 9 a.m. to 9 p.m. (ET).

- Get one-on-one personalized support and information about blood cancers
- Know the questions to ask your doctor
- Discuss financial resources
- Receive individualized clinical-trial searches

Contact us at  
**800-955-4572** or  
[www.LLS.org/  
InformationSpecialists](http://www.LLS.org/InformationSpecialists)  
(Language interpreters can be requested.)





For more information, please contact our Information Specialists **800.955.4572** (Language interpreters available upon request).

**National Office** 3 International Drive, Suite 200 Rye Brook, NY 10573

The mission of The Leukemia & Lymphoma Society (LLS) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families. Find out more at [www.LLS.org](http://www.LLS.org).